Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

November 30, 2004

These guidelines were developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Resource Center at the François-Xavier Bagnoud Center, UMDNJ.
The Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH).

It is recognized that guidelines for antiretroviral use in pediatric patients are rapidly evolving. The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children will review new data on an ongoing basis and provide regular updates to the guidelines, and the most recent information is available on the ***AIDSinfo*** **Web site** (**http://aidsinfo.nih.gov/**).

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The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Resource Center at the François-Xavier Bagnoud Center, UMDNJ,
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SUMMARY

Although the pathogenesis of human immunodeficiency virus (HIV) infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons, there are unique considerations needed for HIV-infected infants, children, and adolescents, including:

a. acquisition of infection through perinatal exposure for many infected children;
b. *in utero*, intrapartum, and/or postpartum neonatal exposure to zidovudine (ZDV) and other antiretroviral medications in most perinatally infected children;
c. requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants under age 15 to 18 months old;
d. age-specific differences in immunologic markers (i.e., $CD4^+$ T cell count);
e. changes in pharmacokinetic parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance;
f. differences in the clinical and virologic manifestations of perinatal HIV infection secondary to the occurrence of primary infection in growing, immunologically immature persons; and
g. special considerations associated with adherence to antiretroviral treatment for infants, children and adolescents.

This report addresses the pediatric-specific issues associated with antiretroviral treatment and provides guidelines to health care providers caring for infected infants, children, and adolescents.* It is recognized that guidelines for antiretroviral use in pediatric patients are rapidly evolving. The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children will review new data on an ongoing basis and provide regular updates to the guidelines; the most recent information is available on the *AIDSinfo* Web site (**http://AIDSinfo.nih.gov**). These guidelines are developed for the United States and may not be applicable in other countries. Guidelines for resource-limited settings can be found at the World Health Organization Web site (**http://www.who.int/hiv/topics/arv/en/**)

INTRODUCTION

In 1993, the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, composed of specialists caring for human immunodeficiency virus (HIV)-infected infants, children, and adolescents, was convened by the François-Xavier Bagnoud Center (FXBC), UMDNJ (**http://www.fxbcenter.org/**). On the basis of available data and a consensus reflecting clinical experience, the Working Group concluded that antiretroviral therapy was indicated for any child with a definitive diagnosis of HIV infection who had evidence of substantial immunodeficiency (based on age-related $CD4^+$ T cell count thresholds) and/or who had HIV-associated symptoms. ZDV monotherapy was recommended as the standard of care for initiation of therapy. Routine antiretroviral therapy for infected children who were asymptomatic or had only minimal symptoms (i.e., isolated lymphadenopathy or hepatomegaly) and normal immune status was not recommended *[1]*.

Since the Working Group developed the 1993 recommendations, dramatic advances in laboratory and clinical research have been made. The rapidity and magnitude of HIV replication during all stages of infection are greater than previously believed and account for the emergence of drug-resistant viral variants when antiretroviral treatment does not maximally suppress replication *[2, 3]*. Assays that quantitate plasma HIV RNA copy number have become available, permitting a sensitive assessment of risk for disease progression and adequacy of antiretroviral therapy. New classes of antiretroviral drugs have become available that have enabled reduction in HIV viral load to levels that are undetectable and have reduced disease progression and mortality in many HIV-infected persons.

* Information included in these guidelines may not represent Food and Drug Administration (FDA) approval or approved labeling for the particular product or indications in question. Specifically, the terms “safe” and “effective” may not be synonymous with the FDA-defined legal standards for product approval.

Therefore, therapeutic strategies now focus on early institution of antiretroviral regimens capable of maximally suppressing viral replication to reduce the development of resistance and to preserve immunologic function. Additionally, the results of Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 have demonstrated that the risk for perinatal HIV transmission can be substantially diminished with the use of a regimen of ZDV administered during pregnancy, during labor, and to the newborn *[4]*. Rates of mother-to-child HIV transmission in the U.S. are currently under 2% due to implementation of recommendations for universal prenatal HIV counseling and testing, widespread use of highly active antiretroviral therapy and elective cesarean delivery by HIV-infected pregnant women, and avoidance of breastfeeding.

These advances in HIV research have led to major changes in the treatment and monitoring of HIV infection in the United States. A summary of the basic principles underlying therapy of HIV-infected persons has been formulated by the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection *[5]*. Treatment recommendations for infected adults and post-pubertal adolescents have been updated by the U.S. Department of Health and Human Services Panel of Clinical Practices for Treatment of HIV Infection *[5]*. This document is regularly updated to reflect the most recent literature. The most recent update is available at **http://AIDSinfo.nih.gov.**

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 persons, there are unique considerations needed for HIV-infected infants, children, and adolescents. Most HIV infections in children are acquired perinatally, and most perinatal transmission occurs during or near the time of birth, which raises the possibility of initiating treatment in an infected infant during the period of initial (i.e., primary) HIV infection (if sensitive diagnostic tests are used to define the infant's infection status early in life). Perinatal HIV infection occurs during the development of the infant's immune system; thus, both the clinical manifestations of HIV infection and the course of immunologic and virologic markers of infection differ from those for adults. Treatment of perinatally infected children will occur in the context of prior exposure to ZDV and other antiretroviral drugs used during pregnancy and the neonatal period, for maternal treatment, to prevent perinatal transmission, or both *[6, 7]*. Additionally, drug pharmacokinetics change during the transition from the newborn period to adulthood, requiring specific evaluation of drug dosing and toxicity in infants and children. Finally, optimizing adherence to therapy in children and adolescents requires specific considerations.

To update the 1993 antiretroviral treatment guidelines for children *[1]* and to provide guidelines for antiretroviral treatment similar to those for HIV-infected adults *[5]*, NPHRC, the Health Resources and Services Administration (HRSA), and NIH reconvened the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, consisting of experts caring for HIV-infected children and adolescents, family members of HIV-infected children, and government agency representatives. The Working Group met in June 1996 and again in July 1997 to establish and finalize new guidelines for the treatment of HIV-infected infants, children, and adolescents. These were initially published in 1998 both in MMWR *[8]*, which is periodically updated, and as a supplement to the journal *Pediatrics [9]*. The supplement included both antiretroviral therapy and management of complications of HIV infection. This material will be accessible by a hyperlink from this document in the near future.

Since 1998, the Working Group has held monthly conference calls to review new data; recommendations for changes to the pediatric treatment guidelines are reviewed by the Working Group and incorporated as appropriate. The most recent guidelines are available on the *AIDSinfo* Web site (**http://AIDSinfo.nih.gov**).

The treatment recommendations provided in this updated report 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 experience of the Working Group members. The Working Group intends the guidelines to be flexible and not to supplant the clinical judgment of experienced health care providers.

BACKGROUND

Concepts Considered in the Formulation of Pediatric Treatment Guidelines

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

- Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their children and to preventing perinatal transmission. Therefore, prenatal HIV counseling and testing with consent should be the standard of care for all pregnant women in the United States *[10-12]*.
- 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.*
- Pharmaceutical companies and the federal government should collaborate to ensure that drug formulations suitable for administration to infants and children are available at the time that new agents are being evaluated in adults.
- 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, irrespective of labeling notations.
- Management of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, management of HIV infection in children and adolescents should be directed by a specialist in the treatment of pediatric and adolescent HIV infection. If this is not possible, such experts should be consulted regularly.
- 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.
- Determination of HIV RNA and $CD4^+$ T cell levels is essential for monitoring and modifying antiretroviral treatment in infected children and adolescents as well as adults; therefore, assays to measure these variables should be monitored on a regular basis.
- Health care providers considering antiretroviral regimens for infants**,** children and adolescents should consider certain factors influencing adherence to therapy, including:
  a. availability and palatability of pediatric formulations;
  b. 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;
  c. 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
  d. potential for drug interactions.
- The choice of antiretroviral regimens should include consideration of factors associated with possible limitation of future treatment options, including 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 is essential for the care of HIV-infected children. Growth failure and neurodevelopmental deterioration may be specific manifestations of HIV infection in children. Nutritional-support therapy is an intervention that affects immune function, quality of life, and bioactivity of antiretroviral drugs.

Identification of Perinatal HIV Exposure

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

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

during pregnancy. Universal HIV counseling and voluntary HIV testing with consent are endorsed by the Working Group and are recommended as the standard of care for all pregnant women in the United States by the Public Health Service (PHS), the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists *[10-12]*.

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

a. HIV-infected women to receive appropriate antiretroviral therapy and prophylaxis against opportunistic infections for their own health;
b. provision of antiretroviral chemoprophylaxis with ZDV during pregnancy, during labor, and to newborns to reduce the risk for HIV transmission from mother to child *[4, 6, 7]*
c. counseling of 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 *[13]*;
d. initiation of prophylaxis against Pneumocystis carinii pneumonia (PCP) in all HIV-exposed infants beginning at age 4 to 6 weeks in accordance with PHS guidelines *[14]*; and
e. early diagnostic evaluation of HIV-exposed infants to permit early initiation of aggressive antiretroviral therapy in infected infants.

If women are not tested for HIV during pregnancy, counseling and HIV testing should be recommended during the immediate postnatal period. When maternal serostatus has not been determined during the prenatal or immediate postpartum period, newborns should undergo HIV antibody testing with counseling and consent of the mother unless state law allows testing without consent *[15]*. The HIV-exposure status of infants should be determined rapidly because the neonatal component of the recommended ZDV chemoprophylaxis regimen should begin as soon as possible after birth and because PCP prophylaxis should be initiated at age 4 to 6 weeks in all infants born to HIV-infected women. Those infants who have been abandoned, are in the custody of the state, or have positive toxicology screening tests should be considered at high risk for exposure to HIV, and mechanisms to facilitate rapid HIV screening of such infants should be developed.

Diagnosis of HIV Infection in Infants

HIV infection can be definitively diagnosed through the use of viral diagnostic assays in most infected infants by age 1 month and in virtually all infected infants by age 6 months. Tests for antibodies to HIV, including newer rapid tests, do not establish the presence of HIV infection in infants because of transfer of maternal antibodies; therefore a virologic test should be utilized *[10]*. A positive virologic test (i.e., detection of HIV by culture, DNA polymerase chain reaction [PCR] or RNA assays) indicates possible HIV infection and should be confirmed by a repeat virologic test on a second specimen as soon as possible after the results of the first test become available. Diagnostic testing should be performed before the infant is age 48 hours, at age 1–2 months, and at age 3–6 months. Additional testing at age 14 days might allow for early detection of infection.

HIV DNA PCR is the preferred virologic method for diagnosing HIV infection during infancy. A meta-analysis of published data from 271 infected children indicated that HIV DNA PCR was sensitive for the diagnosis of HIV infection during the neonatal period. Thirty-eight percent (90% confidence interval [CI] = 29%–46%) of infected children had positive HIV DNA PCR tests by age 48 hours *[16]*. 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 PCR by age 14 days. By age 28 days, HIV DNA PCR has 96% sensitivity and 99% specificity to identify HIV proviral DNA in peripheral blood mononuclear cells (PBMCs) *[16]*.

Assays that detect HIV RNA in plasma appear to be 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 *[17-22]*. 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 should be interpreted with caution. Combined use of HIV DNA PCR and HIV RNA assays for infant diagnosis has not been studied, but some clinicians choose to use an HIV RNA assay as the confirmatory test for infants testing HIV DNA PCR positive. 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 culture for the diagnosis of infection has a sensitivity that is similar to that of HIV DNA PCR *[23]*. However, HIV culture is more complex and expensive to perform than DNA PCR, and definitive results may not be available for 2–4 weeks. Although both standard and immune-complex-dissociated p24 antigen tests are highly specific for HIV infection and have been used to diagnose infection in children, the sensitivity of these tests is less than that of other HIV virologic tests. The use of p24 antigen testing alone is not recommended to exclude infection or for diagnosis of infection in infants aged less than a month because of a high frequency of false-positive assays during this time *[24]*.

Initial testing is recommended by age 48 hours because as many as 40% of infected infants can be identified at this time. 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 for 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 *[25]*. Some researchers have proposed that infants with early infection may have more rapid disease progression than those with late infection and therefore should receive a more aggressive therapeutic approach *[25, 26]*. However, recent 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 *[27]*. HIV RNA copy number after the first month of life was more prognostic of rapid disease progression than the time at which HIV culture tests were positive *[27]*. Repeat diagnostic testing also can be considered at age 14 days in infants with negative tests at birth, because the diagnostic sensitivity of virologic assays increases rapidly by age 2 weeks, and early identification of infection would permit discontinuation of neonatal ZDV chemoprophylaxis and further evaluation of the need for more aggressive combination antiretroviral therapy (see **When to Initiate Therapy in HIV-Infected Infants Under Age 12 Months** and **Table 6**).

Infants with initially negative virologic tests should be re-tested at age 1 to 2 months. With increasing use of ZDV to reduce perinatal transmission, most HIV-exposed neonates will receive 6 weeks of antiretroviral chemoprophylaxis. Although prophylactic antiretroviral therapy theoretically could affect the predictive value of HIV virologic testing in neonates, ZDV 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 *[4, 20-22, 28]*. Whether the current, more intensive combination antiretroviral regimens women may receive during pregnancy for treatment of their own HIV infection will affect diagnostic test sensitivity in their infants is unknown. Similarly, if more complex regimens are administered to HIV-exposed infants for perinatal prophylaxis, the sensitivity of diagnostic assays will need to be re-examined.

HIV-exposed children who have had repeatedly negative virologic assays at birth and at age 1 to 2 months should be retested at age 3 to 6 months. HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples, regardless of age. HIV infection can be reasonably excluded in non-breast fed infants with two or more negative virologic tests performed at age $\geq$1 month, with one of those being performed at age $\geq$ 4 months *[14]*. Two or more negative HIV immunoglobulin G (IgG) antibody tests performed at age >6 months with an interval of at least 1 month between the tests also can be used to reasonably exclude HIV infection in HIV-exposed children with no clinical or virologic laboratory evidence of HIV infection. Serology after 12 months is recommended 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 12 months, then testing should be repeated between 15-18 months *[29]*. Loss of HIV antibody in a child with previously negative HIV DNA PCR tests definitively confirms that the child is HIV uninfected. A positive HIV antibody test at >18 months of age indicates HIV infection *[10]*.

Although HIV subtype B is the predominant viral subtype found in the U.S., 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 SE Asia *[21]*. Currently available HIV DNA PCR tests are less sensitive for detection for non-subtype B HIV, and false negative HIV DNA PCR assays have been reported in infants infected with non-subtype B HIV *[30-32]*.

Caution should be exercised in the interpretation of negative HIV DNA PCR test results in infants born to mothers who may have acquired an HIV non-B subtype. Some of the currently available HIV RNA assays have improved sensitivity for detection of non-subtype B HIV infection *[33-35]*, although even these assays may not detect some non-B subtypes, particularly group O HIV strains *[36]*. In cases of infants where 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 to detecting non-subtype B HIV is recommended (for example, the Amplicor HIV-1 monitor test 1.5, Nuclisens HIV-1 qt, or Quantiplex HIV RNA 3.0 (bDNA) assays). 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 18 months of age.

MONITORING OF PEDIATRIC HIV INFECTION

Immunologic Parameters in Children

Clinicians interpreting $CD4^+$ T cell count for children must consider age as a variable. $CD4^+$ T cell 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 6 years *[37, 38]*. A pediatric clinical and immunologic staging system for HIV infection has been developed that includes age-related definitions of immune suppression (**Table 1** and **Table 2**) *[39]*. Although the $CD4^+$ T cell absolute count that identifies a specific level of immune suppression changes with age, the $CD4^+$ T cell percentage that defines each immunologic category does not. Thus, a change in $CD4^+$ percentage, not number, may be a better marker of identifying disease progression in children. In infected children and adults, the $CD4^+$ T cell count declines as HIV infection progresses, and patients with lower $CD4^+$ T cell counts have a poorer prognosis than patients with higher counts (**Table 3**).

Because knowledge of immune status (i.e., $CD4^+$ T cell count and percentage) is essential when caring for HIV-infected infants and children, $CD4^+$ T cell values should be obtained as soon as possible after a child has a positive virologic test for HIV and every 3 months thereafter *[40, 41]*. Increased frequency of evaluations may be needed for children experiencing immunologic or clinical deterioration or to confirm an abnormal value. Infected infants who have a thymic defect lymphocyte immunophenotypic profile (i.e., $CD4^+$ T cell count <1,900/mm^3 and $CD8^+$ T cell count $\leq$850/mm^3) during the first 6 months of life have had more rapid HIV disease progression than infants who do not have this profile *[42]*.

The prognostic value of $CD4^+$ T cell percentage and HIV RNA copy number was assessed in a large individual patient meta-analysis that incorporated clinical and laboratory data from 17 pediatric studies and included 3,941 HIV-infected children receiving either no therapy or only zidovudine monotherapy *[43]*. 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 $CD4^+$ T cell percent and HIV RNA copy number at baseline. **Figures 1** and **2** and **Table 3** depict age-associated one-year risk for developing AIDS or death as a function of $CD4^+$ cell percentage. The one-year risk of AIDS is <10% and death is <2% for children over age one year who have $CD4^+$ cell percentage $\geq$25%. However, infants during the first year of life experience proportionately higher risks. For example, comparing a one year old child with $CD4^+$ T cell percentage of 25% to a five year old child with the same $CD4^+$ T cell percentage, there is an approximate fourfold increase in the risk of AIDS and sixfold increase in the risk of death in the one year old child (**Figure 1**). However, all age groups demonstrate rapid increases in risk as $CD4^+$ cell percentage decreases below 15-20%. 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"**). A website 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 according to age and the most recent $CD4^+$ T cell percentage or HIV-1 RNA viral load measurement in HIV-infected children in the absence of effective antiretroviral therapy (URL: **http://www.pentatrials.org/hppmcs**) *[43]*.

The $CD4^+$ T cell count or percentage value is used in conjunction with other measurements to guide antiretroviral treatment decisions and primary prophylaxis for PCP after age one year. However, measurement of $CD4^+$ T cell values can be associated with considerable intrapatient variation. Even mild intercurrent illness or the receipt of vaccinations can produce a transient decrease in $CD4^+$ T cell count and percentage; thus, $CD4^+$ T cell values are best measured when patients are clinically stable. No modification in therapy should be made in response to a change in $CD4^+$ T cell values until the change has been substantiated by at least a second determination, with a minimum of 1 week between measurements.

HIV RNA in Children

Viral burden in peripheral blood can be determined by using quantitative HIV RNA assays. During the period of primary infection in adults, HIV RNA copy number initially rises to high peak levels. Coincident with the body's humoral and cell-mediated immune response, RNA levels decline by as much as 2–3 $\log_{10}$ copies to reach a stable lower level (i.e., the virologic set-point) approximately 6 to 12 months following acute infection, reflecting the balance between ongoing viral production and immune elimination *[44, 45]*. Several studies conducted among adults have indicated that infected persons with lower HIV copy number at the time of RNA stabilization have slower progression and improved survival compared with those with high HIV RNA set points *[46, 47]*. On the basis of such data, recommendations for the use of HIV RNA copy number in deciding to initiate and change antiretroviral therapy in infected adults have been developed *[5]*. These recommendations also are applicable to infected adolescents, particularly those who have acquired HIV infection recently rather than through perinatal infection. These recommendations also are likely to be applicable to perinatally infected children aged >3 years.

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 *[48, 49]*. 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 *[27]*. Additionally, in contrast to the adult pattern, after the first year of life, HIV RNA copy number slowly declines over the next few years of life *[27, 50-52]*. 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.

Some data indicate that high HIV RNA levels (i.e., >299,000 copies/mL) in infants aged <12 months may be correlated with disease progression and death; however, RNA levels in infants who have rapid disease progression and those who do not overlap considerably *[27, 49]*. High RNA levels (i.e., levels of >100,000 copies/mL) in infants also have been associated with high risk for disease progression and mortality, particularly if $CD4^+$ T cell percentage is <15% *[51]* (**Table 4**). Similar findings have been reported in a preliminary analysis of data from PACTG protocol 152 correlating baseline virologic data with risk for disease progression or death during study follow up *[52]*. In this study, the relative risk for disease progression was reduced by 54% for each 1 $\log_{10}$ decrease in baseline HIV RNA level.

The most robust data set available to elucidate the predictive value of plasma RNA for disease progression in children was assembled in the individual patient meta-analysis discussed earlier, the HIV Pediatric Prognostic Markers Collaborative Study (see section on **Immunologic Parameters in Children**) *[43]*. As for $CD4^+$T cell percentage, analyses were performed for age-associated risk in the context of plasma RNA levels. Similar to data from previous studies *[51, 52]*, the risk of clinical progression to AIDS or death dramatically increases when HIV RNA exceeds 100,000 copies (5.0 $\log_{10}$ copies)/mL; at lower values, only older children show much variation in risk (**Figures 3** and **4** and **Table 3**). However, the relationship between plasma virus and risk approached a more linear association than for $CD4^+$ percentage, resulting in more difficulty in assigning risk thresholds. 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 observed for the $CD4^+$ percentage data.

Despite data indicating that high RNA levels are associated with disease progression, the predictive value of specific HIV RNA levels for disease progression and death for an individual child is

moderate *[51]*. HIV RNA levels may be difficult to interpret during the first year of life, because levels are high and there is marked overlap in levels between children who have and those who do not have rapid disease progression *[48]*. Additional data indicate that $CD4^+$ T cell percentage at baseline, HIV RNA copy number at baseline, and changes in these parameters over time assist in determining the mortality risk in infected children, and the use of the two markers together may more accurately define prognosis *[51, 52]*. Similar data and conclusions have been reported from several studies involving infected adults *[53-55]*.

HIV RNA and $CD4^+$ percentage provide complementary and independent information about prognosis for HIV-infected children (**Table 4**), and measurement of HIV RNA levels, like $CD4^+$ percentage, is an important component of care for HIV-infected infants and children. HIV RNA copy number should be assessed as soon as possible after a child has a positive virologic test for HIV and every three to four months thereafter; increased frequency of evaluations may be needed for children experiencing virologic or clinical deterioration, to confirm an abnormal value, or when initiating or changing antiretroviral therapy (see section **Virologic Considerations for Changing Therapy**).

Methodologic Considerations in the Interpretation and Comparability of HIV RNA Assays

The use of HIV RNA assays for clinical purposes requires specific considerations *[56]*, which are discussed more completely elsewhere *[5]*. 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 twofold (0.3 log10) or more *[57-60]*. There are currently three FDA-approved viral load assays:

- HIV-1 reverse transcriptase quantitative polymerase chain reaction assay (Amplicor HIV-1 Monitor® Test, version 1.5, Roche Diagnostics);
- HIV-1 nucleic acid sequence-based amplification test (NucliSens® HIV-1 QT, bioMerieux); and
- HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay (VERSANT® HIV-1 RNA 3.0 Assay [bDNA]).

The first two assays have a lower limit of detection of 50 copies/mL, while the bDNA assay has an approved lower limit of detection of 75 copies/mL. 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.

The predominant virus subtype or clade in the United States is clade 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/clades *[34, 35]*. This is important for many regions of the world with other predominant clades as well as for the U.S. where a small subset of individuals are infected with clades prevalent in other parts of the world *[30-32]*. 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 (i.e., 100 µL of plasma), followed by the Amplicor HIV-1 Monitor™ (i.e., 200 µL of plasma) and the VERSANT® assays (i.e., 1 mL of plasma).

Biologic variation in HIV RNA levels within one person is well documented, and repeated measurement of HIV RNA levels in a clinically stable infected adult can vary by as much as threefold (0.5 $\log_{10}$) in either direction over the course of a day or on different days *[5, 55, 60]*. 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 *[27, 50, 51]*. 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 to 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 greater than fivefold (0.7 $\log_{10}$) in infants aged <2 years and greater than threefold (0.5 $\log_{10}$) in children aged $\geq$2 years after repeated testing should be considered reflective of a biologically and clinically substantial change. To reduce the impact of assay variability in the clinical management of patients, two samples can be obtained at baseline and the average of the two 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.

Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents

HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start and what antiretroviral medications should be used.

Adult guidelines for antiretroviral therapy are usually appropriate for postpubertal adolescents because HIV-infected adolescents who were infected sexually or through injecting-drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children *[5]*. The immunopathogenesis and virologic course of HIV infection in adolescents is being defined. Most adolescents have been infected during their teenage years and are in an early stage of infection, making them potential candidates for early intervention. A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or through blood products as young children. Such adolescents may have a unique clinical course that differs from that of adolescents infected later in life *[61]*.

Because many adolescents with HIV infection are sexually active, contraception and prevention of HIV transmission should be discussed with the adolescent. The potential for pregnancy may also alter choice of antiretroviral therapy. As an example, efavirenz should be used with caution in females of child bearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, pregnancy testing, close monitoring and a commitment on the part of the teen to use effective contraception.

Dosages of medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty *[62]* and not on the basis of age *[40]*. Adolescents in early puberty (i.e., Tanner Stage I and II) should be administered doses using pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. Because puberty may be delayed in perinatally-HIV-infected children, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are considerably higher than usual adult doses. Since data are not available to predict optimal medication doses for each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt (i.e., Tanner Stage III in females and Tanner Stage IV in males) using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity.

Puberty is a time of somatic growth and sex differentiation, with females developing more body fat and males more muscle mass. Although these physiologic changes theoretically could affect drug pharmacokinetics (especially for drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors), no clinically consequential impact has been noted with nucleoside analogue reverse transcriptase inhibitor (NRTI) antiretroviral drugs *[63]*. Efficacy and pharmacokinetic clinical trial data with PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) during the transition period of adolescence are more limited.

Specific Issues of Adherence for HIV-Infected Children and Adolescents

Background

Medication adherence is fundamental to successful antiretroviral therapy. Studies of both children and adults clearly demonstrate that adherence is a major factor determining the degree of viral suppression achieved in response to antiretroviral therapy. *[64-66]* Poor adherence often leads to virologic failure. Prospective adult studies have shown the risk of virologic failure to increase as the proportion of missed doses increases over time *[64, 67]*. Subtherapeutic antiretroviral drug levels resulting

from poor adherence may enhance the development of drug resistance to one or more drugs in a given regimen, and possible cross-resistance to other drugs in the same class. Therefore, 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. In a randomized treatment trial, caregivers reported that 30% of children missed one or more doses of antiretroviral medications in the preceding 3 days *[65]*; 42% of caregivers in an observational study reported at least one missed dose in the past week *[68]*. Using pharmacy refills to measure adherence, a study at a site with a comprehensive, multidisciplinary adherence program noted that only 42 of 72 children (58%) had refill rates of at least 75% over 6 months *[66]*. A study of another clinical program found that refill rates of 90% or greater adherence were met for only 12 of 35 children (34%) over one year *[69]*. These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence assessment, education, and support integral components of care.

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient factors, and characteristics of healthcare providers. A number of these factors pose special problems in children. Liquid formulations or formulations suitable for mixing with formula or food are necessary for administration of oral drugs to young children. Lack of palatability of such formulations can be problematic depending on the child's willingness and ability to accept and retain the medication. Absorption of some antiretroviral drugs can be affected by food, and attempting to time the administration of drugs around meals can be difficult for caregivers of young infants who require frequent feedings. Infants and young children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments and the ability and willingness of the child to take the drug. Some caregivers may place too much responsibility on older children and adolescents for managing medications. Many other barriers to adherence to drug regimens exist for children and adolescents with HIV infection. For example, unwillingness of the caregivers to disclose their child's HIV infection status to others may create specific problems, including reluctance of caregivers to fill prescriptions in their home neighborhood, hiding or relabeling medications to maintain secrecy within the home, reduction of social support (a variable associated with diminished treatment adherence), and a tendency to eliminate midday doses when the parent is away from the home or the child is at school. Factors that act as barriers to adherence also provide targets for interventions.

Adherence Assessment and Monitoring

The process of adherence assessment should begin before therapy is initiated and 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 individualized needs for intervention. Assessment should focus on establishing a dialogue and a partnership in medication management. Specific, but open-ended questions should be used to elicit information about past experience and concerns about antiretroviral therapy even when starting medications for the first time, since caregivers may have taken these medications or heard about them from others. Interviews and/or written assessment tools can be used to identify factors that make it difficult for children to receive medication as prescribed as well as those that make it easier to administer medications. When assessing readiness 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. Yet regular monitoring is key to early identification of problems and can reinforce the importance of taking medications as prescribed. Useful methods include self-report by caregivers, and children when indicated, pharmacy refill checks and pill counts. Electronic monitoring devices, such as Medication Event Monitoring Systems or MEMS caps, record opening of medication bottles on a computer chip in the cap *[70]*. MEMS caps have been shown to be useful research tools to measure adherence, but have little role in the clinical setting.

Both caregivers and providers often overestimate adherence. To improve the accuracy of recall, focus self-report on recent missed doses over a three-day or one week period. Asking caregivers to name and/or describe the regimen is also helpful. It is important for clinicians to recognize that nonadherence is a common problem and that it can be difficult for clients to share information about missed doses or prescriptions that were not filled. A non-judgmental attitude and trusting relationship can foster more open communication and facilitate assessment. Use of multiple methods is recommended, since the ability to name and describe medications, pharmacy refills or pill counts may identify adherence problems not evident from self-reports. 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 report. Therefore, clinical judgment is required to best interpret adherence information obtained from multiple sources *[71]*.

Because past medication taking behaviors often predict future adherence, it is especially important to identify adherence problems, define contributing factors, and intervene to improve adherence prior to changing medications for virologic failure. Surrogate markers of HIV RNA levels and $CD4^+$ lymphocyte counts are important adjuncts in adherence assessment. But studies indicate that children with a clinical response to therapy may have adherence problems while those who maintain good adherence may experience virologic failure *[65, 66, 68, 69]*. It is not always possible to document suspected nonadherence, particularly in outpatient settings. Home visits can play an important role, and in some cases, suspected nonadherence is confirmed only when dramatic clinical responses to antiretroviral therapy occur during hospitalizations or in other supervised settings *[72]*. Preliminary studies suggest that monitoring plasma concentrations of protease inhibitors, or therapeutic drug monitoring, may be a useful method to identify nonadherence, but this approach remains investigational *[73]*.

Strategies to Improve and Support Adherence

Many strategies can be used to increase medication adherence, including development of patient-focused treatment plans to accommodate specific patient needs and mobilization of social and community support services. Intensive follow-up is required, particularly during the critical first few months after therapy is started; patients should be seen frequently to assess adherence, drug tolerance, and virologic response. Coordinated, comprehensive, family-centered systems of care often can address many of the daily problems that may affect adherence to complex medical regimens. For some families, certain issues (i.e., a safe physical environment and adequate food and housing) may take priority over medication administration and need to be resolved. Case managers, mental-health counselors, peer educators, outreach workers, and other members of the multidisciplinary team often may be able to address specific barriers to adherence. Evidence suggests that multifaceted approaches, rather than one specific intervention are most effective *[74]*. These can include regimen-related strategies; educational, behavioral and supportive strategies focused on children and families, and strategies that focus on healthcare providers *[75]*. **Table 5** summarizes some of the strategies that can be used to support and improve adherence with antiretroviral medications.

Regimen-Related Strategies

Delivering antiretroviral treatment to children can be made difficult by the often stringent requirements of highly active regimens, which may require the administration of large numbers of pills, or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. Especially when the caregiver her or himself also faces chronic illness, helping the child to take medications can be daunting. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, frequency of therapy, and minimizing drug interactions and side effects. When non-adherence has become a problem, addressing medication-related issues may result in improvement. Medication side effects may cause non-adherence and may need to be managed. If a regimen is overly complex, it may be simplified. For example, adherence is often enhanced by changing from a thrice daily dosing schedule to twice daily dosing. When the burden of pills is too great for a child, often one or more drugs can be changed resulting in a regimen containing fewer pills. When non-adherence is related to poor palatability of a liquid formulation or crushed pills, the offending taste can often be masked, or the child may be taught to swallow pills in order to overcome medication aversion *[76]*.

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, 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 HAART 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 both times and doses of medications, and demonstration of the use of syringes, medication cups and pill boxes. These adherence tools are of general benefit, and should be considered for all caregivers who provide HIV medications to children, and especially emphasized for those caregivers who are neurologically or cognitively impaired.

In addition to caregiver education, 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 *[77]*. In cases of non-adherent children with significant behavioral problems which interfere with the child taking medications, family-provider meetings structured to discuss such problems and identify potential solutions can be helpful. For non-adherent infants and young children who are at-risk for disease progression and for whom aversion to taking medications is severe and persistent, a gastrostomy tube may be considered. Gastrostomy tube placement has been shown to enhance HIV medication adherence in a select group of children with adherence difficulties *[78]*. Benefits included reduced medication administration time and improved behavior around taking medications. Home nursing interventions may be beneficial where adequate resources are available *[79]*. In cases of medical, psychological or social impairment of the caregiver, nurse or home health aid visits to the home for purposes of adherence assessment, education and directly observed dosing may be beneficial. Directly observed dosing of antiretroviral medications has been implemented in adults with promising results *[80]*, and such an approach may also be considered for children. Directly observed treatment strategies for caregivers of children should be educational and supportive in nature rather than punitive.

Healthcare Provider-Related Strategies

While many aspects of adherence seem outside the realm of control, providers have the ability to improve adherence through their own behaviors. This process begins early in the provider's relationship with the family when the clinician obtains explicit agreement to the medication and treatment plan and any further strategies to support adherence. Abilities to foster a trusting relationship and engage 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, commitment to follow-up and high job satisfaction. Several online resources are available to assist HIV healthcare providers to become knowledgeable about adherence, the factors affecting it, as well as strategies to support and improve adherence in children, youth and adults: **http://www.hivguidelines.org/public_html/center/best-practices/treatment_adherence/pdf/treat_adherence_full.pdf**; **http://www.hivfiles.org**; **http://www.hivguidelines.org/public_html/center/clinical-guidelines/ped_adolescent_hiv_guidelines/html/peds_supportive_care/pdf/supportive_care.pdf**.

Adherence Issues for Adolescents

HIV-infected adolescents face specific adherence problems and challenges. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems. HIV-infected adolescents face challenges in adhering to medical regimens for many reasons. Denial and fear of their HIV infection is common, especially in recently diagnosed youth. 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. Furthermore, HIV infected adolescents commonly suffer from low self-esteem, often have unstructured and chaotic lifestyles, and may cope poorly with their illness due to a lack of familial and social

support. 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.

Developmental issues make caring for adolescents unique. The adolescent's approach to illness is often different from that of an adult. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence with 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 to whom they have not yet disclosed their HIV status and those who are homeless and have no place to store medicine.

There are few reports describing adherence to antiretroviral medications in adolescents. One study from a multidisciplinary adolescent HIV clinic indicated that only 61% of patients reported >90% adherence to their medications in the past 90 days *[81]*. The most common reason for non-adherence in this cohort was "too many pills", suggesting that finding simple regimens with low pill burdens are important to youth. Interventions to promote long-term adherence to antiretroviral treatment have not been rigorously evaluated in adolescents. However, preliminary data suggest that interventions based on the "stages of change" model, which assesses adolescents' readiness to adhere to medications, may be effective *[82]*. An intervention approach involving both family and peers to increase adherence in HIV positive youth appears to be effective *[83]*. In clinical practice, the use of reminder systems, such as beepers and alarm devices are popular with some youth. Adolescents may appreciate being provided with small discrete pill boxes in which to store their medications in an organized fashion *[84]*.

TREATMENT RECOMMENDATIONS

General Considerations

Antiretroviral therapy has provided substantial clinical benefit to HIV-infected children with immunologic or clinical symptoms of HIV infection, particularly as more potent therapies have become available. Initial clinical trials of monotherapy with ZDV, didanosine (ddI), lamivudine (3TC), or stavudine (d4T) demonstrated substantial improvements in neurodevelopment, growth, and immunologic and/or virologic status *[85-90]*. Subsequent pediatric clinical trials in symptomatic, antiretroviral-naïve children have demonstrated that combination therapy with either ZDV and 3TC or ZDV and ddI is clinically, immunologically, and virologically superior to monotherapy with ddI or ZDV as initial therapy *[48, 91, 92]*. In clinical trials in antiretroviral-experienced children, combination therapy that included a protease inhibitor was shown to be virologically and immunologically superior to dual nucleoside combination therapy *[93-95]*.

The recognition of the enhanced potency of combination therapy and the identification of new viral targets and classes of antiretroviral agents has led to improvements in antiretroviral therapy that have been accompanied by enhanced survival of HIV-infected children and a reduction in opportunistic infections and other complications of HIV infection. This was demonstrated in a prospective longitudinal cohort study, PACTG 219, which started enrollment prior to the availability of protease inhibitor therapy. The increased use of protease inhibitor-containing therapy (from 0% prior to 1996 to over 70% by 1998) was accompanied by a substantial decrease in mortality: mortality decreased from 5% in 1995/1996 to only 1% in 1997/1998 *[96]*. Similar reductions in mortality with introduction of combination highly active antiretroviral therapy (HAART) in HIV-infected children in Europe have also been reported *[97-99]*.

The following recommendations are meant to provide general guidance for decisions related to treatment of HIV-infected children, and flexibility should be exercised according to the child's individual circumstances. Guidelines for when to start antiretroviral therapy and the choice of drug regimens are evolving. Treatment with HAART has had a dramatic impact on the health of HIV-infected children. However, attainment of these benefits requires rigorous adherence to demanding treatment schedules. Additionally, therapy is associated with short- and long-term toxicities, some of which are only now beginning to be appreciated in children *[100, 101]*. Whenever possible, decisions regarding the management of pediatric HIV infection should be directed by, or in consultation with, a specialist in pediatric and adolescent HIV infection.

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-review journals or in abstract form, with attention to data from pediatric populations when available.

When to Initiate Therapy (Tables 6 and 7)

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

- Severity of HIV disease and risk of disease progression as determined by presence or history of HIV-related serious or AIDS-defining illnesses, and the child's $CD4^+$ cell count and plasma HIV RNA level;
- Availability of appropriate (and palatable) drug formulations for the child 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 co-morbidity that could affect drug choice, such as tuberculosis, hepatitis B or C infection, or chronic renal or liver disease (for example, coadministration of rifampin can significantly reduce drug levels of nevirapine and most protease inhibitors; viral hepatitis can predispose to hepatic toxicity of nucleoside and non-nucleoside antiretroviral drugs; and, depending upon the route of metabolism/excretion for individual drugs, dose modification may be required for individuals with significant renal/liver disease);
- Potential antiretroviral drug interactions with other medications required by the child; and
- The ability of the caregiver and child to adhere to the regimen.

Issues associated with adherence to treatment are especially important in considering whether and when to initiate therapy. Antiretroviral therapy is likely to be most effective in patients who are naïve to treatment and who therefore are less likely to have antiretroviral-resistant viral strains. Lack of adherence to prescribed regimens and subtherapeutic levels of antiretroviral medications, particularly protease inhibitors, may enhance the development of drug resistance and likelihood of virologic failure *[66, 68]*. Participation by the caregivers and child in the decision-making process is crucial, especially in situations for which definitive data concerning efficacy are not available. 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.

The choice whether to start therapy early, while an individual is still asymptomatic, versus delaying therapy until clinical or immunologic symptoms appear, continues to generate considerable controversy among pediatric and adult HIV experts *[102]*. 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.

Guidelines for initiation of therapy in adults have become more conservative over time; treatment is currently recommended for adults with AIDS or severe symptoms and for asymptomatic adults with $CD4^+$ cell count $\leq 200/mm^3$ *[5]*. The adult guidelines

suggest that treatment be considered for individuals with $CD4^+$ cell count between 200-350/mm^3 or plasma HIV RNA levels ≥55,000 copies/mL, while therapy could be deferred in individuals with $CD4^+$ cell count >350/mm^3 and plasma HIV RNA levels <55,000 copies/mL. Because HIV disease progression in children is more rapid than in adults, and laboratory parameters are less predictive of risk for disease progression, particularly for young infants, treatment recommendations have been more aggressive in children than in adults.

HIV-Infected Infants Under Age 12 Months (Table 6)

The risk of disease progression is inversely correlated with the age of the child, with the youngest children at greatest risk for 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 more recent reports, with follow-up through 1999, high rates of progression continue to be observed in young infants, with development of AIDS or death in 15% of HIV-infected children by age 12 months *[99]*. 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 *[99]*. In a meta-analysis of 8 cohort studies and 9 clinical trials in the U.S. and Europe that included nearly 4,000 untreated, infected children, 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 under age 12 months *[43]*.

Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk for rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. Plasma HIV RNA levels are much higher in HIV-infected infants than older infected children and adults, and the predictive value of specific HIV RNA levels for disease progression are more difficult to interpret in infants <12 months old *[27, 52]*. In a large prospective cohort, the median HIV RNA level during the first 2 months of life was 299,000 copies/mL, and the median average viral burden during the first year of life was 185,000 copies/mL *[27]*. While progression to AIDS or death was more frequent in infants with HIV RNA levels above the median, there was considerable overlap in values between those who had rapid disease progression and those who did not. There was no "at risk" viral threshold identified. Additionally, progression of HIV disease and opportunistic infections can occur in young infants with normal $CD4^+$ cell counts *[43]*.

Identification of HIV infection during the first few months of life permits clinicians to initiate antiretroviral therapy or intensify ongoing antiretroviral therapy used for chemoprophylaxis of perinatal transmission during the initial phases of primary infection. However, there are only limited data to address the efficacy of aggressive therapy for HIV-infected infants. Analyses from a large prospective study of 360 HIV-infected U.S. children (Perinatal AIDS Collaborative Transmission Study, PACTS) showed that infants who received early treatment with HAART 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 *[103]*. 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; the proportion of children in these studies with viral levels remaining below quantification after 24 months of therapy ranged from 18% to 62% *[94, 104-108]*. In those infants who have had 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 *[109-111]*.

There are potential problems with universal therapy for infants. Definitive clinical trial data documenting therapeutic benefit from this approach are not currently available. Studies in both adults and children suggest that optimal benefit is achieved with the first antiretroviral treatment regimen, but 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. This can result in substantial differences in antiretroviral dose requirements

between young infants and older children; for example, data from clinical trials indicate that higher nelfinavir and ritonavir doses are required in infants to achieve therapeutic drug levels *[105, 112]*. Resistance to antiretroviral drugs can develop rapidly (particularly in the setting of high viral replication, as observed in infected infants) when drug concentrations are sub-therapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence. Issues associated with adherence must be fully assessed and discussed with the HIV-infected infant's caregivers before the decision to initiate therapy is made. Finally, the possibility of toxicities such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction with prolonged therapy is a concern *[100, 101]*. These concerns are particularly relevant because life-long administration of therapy may be necessary.

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. The Working Group recommends initiation of therapy for infants under age 12 months who have clinical or immunologic symptoms of HIV disease, regardless of HIV RNA level, and consideration of therapy for HIV-infected infants under age 12 months who are asymptomatic and have normal immune parameters (**Table 6**). Because of the high risk for rapid progression of HIV disease, many experts would treat all HIV-infected infants <12 months old, regardless of clinical, immunologic, or virologic parameters. Other experts would treat all infected infants <6 months old, and use clinical and immunologic parameters and assessment of adherence issues for decisions regarding initiation of therapy in infants 6 to 12 months of age. 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 *[103]*.

HIV-Infected Children Aged 12 Months or Older (Table 7)

Since the risk of disease progression slows in children over age 1 year, the option of deferring treatment can be considered for older children. While antiretroviral therapy is indicated for children with symptomatic HIV infection, independent of immunologic and virologic parameters, the degree of clinical symptoms suggesting a need for therapy is unclear. It is clear that children with clinical AIDS (Clinical Category C) or severe immune suppression (Immune Category 3) are at high risk of progression and death, and treatment is recommended for all such children, regardless of virologic status. However, children over age 12 months with mild to moderate clinical symptoms (Clinical Category A or B) or moderate immune suppression (Immune Category 2) are at lower risk for progression than those with severe clinical and immunologic findings *[113]*. In children with mild-moderate clinical symptoms or immune suppression, the level of plasma HIV RNA may provide useful information in terms of risk for progression. Although the level of HIV RNA considered indicative of increased risk for disease progression is not well defined for infants, as discussed above, studies have shown that older children with HIV RNA levels of ≥100,000 copies/mL are at high risk for mortality *[51, 52]*. In the U.S. and European meta-analysis discussed earlier, the 1-year risk of progression to AIDS or death rose sharply for children older than 1 year of age when HIV RNA levels were ≥100,000 copies/mL *[43]*. 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 RNA was 1,000,000 copies/mL.

The Working Group recommends that treatment should be started for all children over age 12 months with AIDS (Clinical Category C) or severe immune suppression (Immune Category 3), and be considered for children who have mild-moderate clinical symptoms (Clinical Categories A or B), moderate immunologic suppression (Immune Category 2), and/or confirmed plasma HIV RNA levels ≥100,000 copies/mL (**Table 7**). Many experts would defer treatment in asymptomatic children aged ≥1 year with normal immune status in situations in which the risk for clinical disease progression is low (e.g., HIV RNA <100,000 copies/mL) and when other factors (i.e., concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, the health care provider should closely monitor virologic, immunologic, and clinical status. Factors to be considered in deciding when to initiate therapy in such children include:

a. Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL);
b. Rapidly declining $CD4^+$ T cell count or percentage to values approaching those indicative of severe immune suppression (i.e., Immune Category 3; see **Table 1**);
c. Development of clinical symptoms; and
d. Ability of caregiver and child to adhere to the prescribed regimen.

CHOICE OF INITIAL ANTIRETROVIRAL THERAPY (Tables 8-11)

General Considerations

Combination therapy is recommended for all infants, children, and adolescents who are treated with antiretroviral agents. When compared with monotherapy, 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.

Monotherapy with the currently available antiretroviral drugs is no longer recommended to treat HIV infection. Use of ZDV 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 ZDV chemoprophylaxis should be changed to a recommended standard combination antiretroviral drug regimen or, if immediate treatment is deferred, ZDV should be discontinued pending therapeutic decisions.

Aggressive antiretroviral therapy with at least three drugs is recommended for initial treatment of infected children 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 a time as possible, while preserving and/or restoring immune function and minimizing drug toxicity.

New drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles most likely will become available, and will increase treatment options for children in the future. 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, as well as palatability problems and potential limitations in subsequent treatment options should resistance develop.

The initial antiretroviral regimen chosen for infected infants theoretically could be influenced by the antiretroviral regimen their mother may have received during pregnancy. However, data from PACTG protocol 076 indicate that ZDV resistance did not account for most infants who became infected despite maternal ZDV treatment *[114, 115]*, and data from PACTG protocol 185 indicate that duration of prior ZDV therapy in women with advanced HIV disease, many of whom received prolonged ZDV before pregnancy, was not associated with diminished ZDV efficacy for reduction of transmission *[116]*. Data do not suggest that the antiretroviral regimen for infected infants should routinely be chosen on the basis of maternal antiretroviral use.

However, continuing to monitor the frequency of antiretroviral-resistant virus among newly infected infants is important. In a retrospective study of the prevalence of antiretroviral drug resistance in a cohort of 91 HIV-infected infants born in 1998 and 1999 in New York State, 11 (12%) infants had provirus with mutations associated with drug resistance; 2% had resistance to drugs in 2 different drug classes *[117]*. History of maternal antiretroviral therapy and infant antiretroviral prophylaxis was not significantly associated with the detection of genotypic resistance in infant virus. However, all six infants with both resistance and perinatal antiretroviral exposure had at least one genotypic mutation conferring resistance to an antiretroviral drug they been exposed to; three of these infants had only intrapartum/neonatal drug exposure. The prevalence of drug resistance among this cohort is similar to the 12-13% observed among recently infected adults in North America *[118, 119]*; in adults with acute HIV infection, consideration of resistance testing prior to initiation of therapy is recommended *[120]*.

The Working Group recommends consideration of resistance testing prior to initiation of therapy in

newly diagnosed infants under age 12 months, particularly if the mother has known or suspected infection with drug-resistant virus. There are no definitive data that demonstrate that resistance testing in this setting correlates with greater success of initial antiretroviral therapy, however.

AVAILABLE ANTIRETROVIRAL DRUGS

As of January 2004, there were 20 antiretroviral drugs approved for use in HIV-infected adults and adolescents; 12 of these have an approved pediatric treatment indication. These drugs fall into several major classes: nucleoside analogue or nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and fusion inhibitors. Brief information on drug formulation, pediatric dosing, and toxicity for the individual drugs can be found in the **Appendix - Characteristics of Available Antiretroviral Drugs.** For more detailed discussion of major classes of antiretroviral drugs and individual drugs for treatment of pediatric HIV infection, go to the **Pediatric Antiretroviral Drug Information** hyperlink**.** The advantages and disadvantages of individual drugs for children are presented in **Tables 8-10**.

Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs) (Table 8)

The NRTIs were the first class of antiretroviral drugs that became available for treatment of HIV infection. These drugs include ZDV, ddI, 3TC, d4T, zalcitabine (ddC), abacavir (ABC), and emtricitabine (FTC). All except ddC and FTC are available in liquid formulations. Additionally, two fixed-dose drug combination preparations are available in solid formulations — a fixed-dose combination of ZDV/3TC (Combivir) and a fixed-dose formulation of ZDV/3TC/ABC (Trizivir). These latter two drug formulations are approved for use in adolescents and adults but are not recommended for use in children less than 12 years old, for whom the adult dosage may not be appropriate.

Dual NRTI combinations form the “backbone” of HAART regimens for both adults and children. Dual NRTI combinations that have been studied in children include ZDV and ddI; ZDV and 3TC; d4T and ddI; d4T and 3TC; ZDV and ddC; and ABC in combination with ZDV, 3TC, d4T or ddI *[91, 121-125]*. The choice of specific dual NRTI combinations for children is based upon the:

- Extent of pediatric experience with the specific drug combination;
- Potency of the NRTI combination;
- Availability of pediatric formulations;
- Potential drug interactions; and
- Short- and long-term toxicity.

The most experience in children is with combination ZDV/3TC, ZDV/ddI, and d4T/3TC, which are the Strongly Recommended dual NRTI combinations for inclusion in initial therapy regimens in children. Alternative dual NRTI combinations include ZDV/ABC, 3TC/ABC, and ddI/3TC. ABC-containing regimens have been shown to be as or possibly more potent than ZDV/3TC *[125]*, but have the potential for ABC-associated life-threatening hypersensitivity reactions in a small proportion of patients *[126, 127]*. Thus, ABC-containing regimens are listed as Alternative rather than as Strongly Recommended dual NRTI combinations for inclusion in initial therapy regimens in children. While the dual NRTI combination of ddI/3TC has been well tolerated, there is less pediatric experience with ddI/3TC than the preferred regimens, and it is thus recommended as an Alternative as well.

The dual NRTI combinations d4T/ddI and ZDV/ddC are recommended for Use in Special Circumstances. In small pediatric studies, d4T/ddI has been shown to have virologic efficacy and was well tolerated *[124, 128]*. However, in studies in adults, d4T/ddI-based combination regimens were associated with greater rates of neurotoxicity, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on ZDV/3TC *[129, 130]*; additionally, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy *[6, 7]*. ZDV/ddC has been studied in children *[123]*, but ddC is less potent than the other NRTI drugs and has greater toxicity, and thus would not be first choice for inclusion in an initial therapy regimen.

Certain dual NRTI drug combinations are Not Recommended. These include ZDV and d4T, due to pharmacologic interactions that can result in potential virologic antagonism, and dual regimens combining ddC with ddI, d4T or 3TC, as pediatric experience

with these combinations is limited and there is overlapping neurotoxicity between the drugs. FTC is approved for use in adults age 18 years or older. Although FTC is under study in children, pharmacokinetic, safety and efficacy data in pediatric patients are not yet available and no pediatric formulation is commercially available. Therefore, there are Insufficient Data to Recommend use of FTC for initial therapy in children.

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs) (Table 8)

Tenofovir disoproxil fumarate is a nucleotide analogue; like the NRTI drugs, tenofovir inhibits HIV reverse transcriptase. However, because the drug already possesses a phosphate molecule, it bypasses the rate-limiting initial phosphorylation step required for activation of NRTIs. Tenofovir was approved for use in combination with other antiretroviral agents for treatment of adults in October 2001; it is not approved for use in pediatric patients <18 years old. The drug is currently in phase I/II studies in the pediatric population, and an oral suspension formulation is under study. However, animal toxicology studies have demonstrated a potential for bone and renal toxicity. Preliminary data from pediatric phase I studies indicate that decreased bone mineral density as measured by dual-energy x-ray absorptiometry (DEXA) scans has been observed in some children. Thus, there are Insufficient Data to Recommend use of this drug for initial therapy in infected children. Given the potential for bone 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. Additionally, a recent study in antiretroviral-naïve adults found suboptimal early virologic response to a regimen containing tenofovir in combination with 3TC and ABC, and this combination regimen should not be used for initial treatment of therapy-naïve adults or children *[131]*.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs) (Table 9)

There are currently 3 NNRTIs approved for treatment of HIV infection: nevirapine, efavirenz, and delavirdine. Nevirapine has a liquid formulation and is approved for pediatric use in children aged 2 months or older. The capsule formulation of efavirenz is approved for use in children over 3 years of age; a liquid formulation is under study and is available through an expanded access program *[132]*. Delavirdine is only available in a tablet preparation and is not approved for use in children. The NNRTI class of drugs rapidly reduces viral load; however, drug resistance develops quickly after initiation of monotherapy or with combination therapy that does not fully suppress viral replication, and cross-resistance between drugs in this class is common. Thus, NNRTI drugs should only be used in the context of a HAART regimen, and never as mono- or dual therapy (with the exception of single-dose nevirapine prophylaxis to reduce mother-to-child HIV transmission *[133]*).

Efavirenz is the Strongly Recommended NNRTI for use in a combination regimen for initial treatment of children over age 3 years who can swallow capsules. Efavirenz in combination with 1 or 2 NRTIs plus nelfinavir has been shown to produce sustained and durable viral suppression in a large proportion of treated children *[134]*. Although there are not data in children, a protease inhibitor-sparing regimen of efavirenz plus 2 NRTIs has had similar efficacy in infected adults *[135]*. Based on these adult data, the latter protease inhibitor-sparing combination offers an alternative to children when issues of adherence or use of protease inhibitors are problematic. There are currently no pharmacokinetic data available on appropriate dosage of efavirenz in children under age 3 years. A liquid preparation has been studied in children over age 3 years *[132]* and is available by expanded access, but only a capsular formulation is currently commercially available. Because efavirenz is currently only available in a capsule, while nevirapine is available in a liquid formulation, for children who require a liquid formulation or who are under age 3 years, nevirapine would be the recommended NNRTI.

For children over age 3 years, nevirapine is Recommended as an Alternative NNRTI for initial therapy. Combination therapy with nevirapine, ZDV and ddI in a small number of young, antiretroviral therapy-naïve infants was associated with substantial and sustained viral suppression in some of the infants *[94, 104]*. Treatment of therapy-naïve adults with nevirapine plus dual NRTI regimen demonstrated comparable results to triple therapy with the protease inhibitor indinavir *[136]*, but no similar comparative studies have been performed in children. Results of studies comparing nevirapine-based versus efavirenz-based regimens in adults are conflicting (see

Recommendation section) 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 *[5, 137, 138]*, nevirapine is therefore Recommended as an Alternative, as opposed to Strongly Recommended, NNRTI for initial treatment of antiretroviral-naïve children, except for those children under age 3 years or who cannot swallow a capsule. Since delavirdine has not been studied in or approved for children, there are Insufficient Data to Recommend it for use as initial therapy in children.

Protease Inhibitors (Table 10)

Protease inhibitors with formulations appropriate for infants and children who cannot swallow pills or capsules include nelfinavir, ritonavir, amprenavir, and lopinavir/ritonavir. Nelfinavir is available as a powder formulation that can be mixed with water or food, while the others are available in liquid formulations. Indinavir, saquinavir, atazanavir, and fosamprenavir are only available in capsule formulations. Two capsule formulations of saquinavir are available: the hard-gel capsule (saquinavir-HGC; Invirase ™) has limited bioavailability, while the soft-gel capsule (saquinavir-SGC; Fortavase ™) has enhanced bioavailability and is the predominant saquinavir formulation now used for therapy. However, both formulations require boosting with ritonavir to achieve adequate levels in children (see below).

Clinical trials involving antiretroviral-naïve children (some as young as 15 days of age) as well as antiretroviral-experienced children provide evidence that the combination of 2 NRTIs and a protease inhibitor may reduce HIV RNA to undetectable levels in a substantial proportion of children *[104, 105, 125, 139-142]* although somewhat less than that observed with similar treatments in infected adults. Nelfinavir, ritonavir, or lopinavir/ritonavir are considered Strongly Recommended protease inhibitors for use in combination with 2 NRTIs as initial therapy in infected children. These drugs have the greatest clinical experience in the pediatric population, and are available in pediatric formulations.

Indinavir and amprenavir when used in combination with 2 NRTIs are Recommended as Alternative protease inhibitors for initial therapy due to more limited experience in children, lack of approved liquid dosage formulations and/or issues of toxicity. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults *[139]*. Amprenavir should not be used in children <4 years of age because of the lack of data for children in this age group, the uncertain impact of extremely high levels of vitamin E found in the liquid formulation (46 IU of vitamin E per mL; the recommended daily dose of vitamin E in children is 10 IU), and the presence of propylene glycol in the oral liquid preparation in a concentration that exceeds WHO standards for use in infants.

Atazanavir is approved for use in HIV-infected adults (in adults, atazanavir coadministration with tenofovir requires low-dose ritonavir boosting to achieve adequate atazanavir drug levels) *[143]*. Although atazanavir is under study in children, pharmacokinetic, safety and efficacy data in pediatric patients are not yet available and no pediatric formulation is commercially available; it is likely that co-administration of atazanavir with a low-dose ritonavir boost will be needed to achieve adequate drug levels in children. Therefore, there are Insufficient Data to Recommend use of atazanavir for initial therapy in children.

Fosamprenavir calcium is a prodrug of amprenavir that is approved for use in combination therapy for HIV-infected adults. Pediatric trials are ongoing at this time, but at present there are Insufficient Data to Recommend use of fosamprenavir for initial therapy in children.

Studies of infected adults have indicated that some drugs that inhibit the cytochrome P450 system, including the protease inhibitor ritonavir, can produce substantial increases in the drug levels of other protease inhibitors. Low-dose, non-therapeutic doses of ritonavir when combined with saquinavir, amprenavir, and indinavir have been shown to act as a pharmacological “booster” to produce elevated therapeutic plasma concentrations of the second drug. The protease inhibitor fixed-dose combination lopinavir/ritonavir is a preparation that takes advantage of this pharmacokinetic enhancement by using a low dose of ritonavir to produce sustained therapeutic levels of lopinavir. However, while combinations of ritonavir with saquinavir-SGC, saquinavir-HGC, indinavir, or nelfinavir in infected adults have shown evidence of virologic suppression when combined with dual NRTIs, these studies have been predominantly conducted among treatment-experienced adults, and it is unclear whether dual protease inhibitors offer any substantial benefit over

a single protease inhibitor for initial therapy of antiretroviral naïve individuals *[144-147]*.

In children, available pharmacokinetic data indicate that administration of saquinavir SGC does not result consistently in efficacious plasma levels, possibly due to increased systemic clearance and reduced oral bioavailability. Therefore, saquinavir should not be used as a sole protease inhibitor in combination therapy in children. To achieve adequate drug levels in children, saquinavir-SGC must be administered with a second protease inhibitor that inhibits saquinavir metabolism (e.g., ritonavir or nelfinavir); however, there are only limited pediatric data on appropriate dosing for such combinations *[148]*. Similarly, saquinavir HGC requires a second protease inhibitor boost to achieve adequate drug levels in children, but no data on appropriate pediatric dosage are available.

Studies of saquinavir in combination with ritonavir or nelfinavir and studies of other dual protease inhibitor combinations are ongoing in treatment-experienced children, but complete data are not yet available *[124, 149, 150]*. Because information on the pharmacokinetics, safety, and efficacy of dual protease inhibitor combinations in children are limited, with the exception of the co-formulated lopinavir/ritonavir, there are Insufficient Data to Recommend use of dual protease inhibitors as a component of initial therapy in children, although such combinations may have utility as a component of secondary treatment regimens for children who have failed initial therapy.

Fusion Inhibitors

A new class of antiretroviral agents called fusion inhibitors inhibit viral binding or fusion to host target cells; enfuvirtide (T-20), the only approved drug in this class, must be administered subcutaneously. Single- and chronic-dosing phase I/II studies of T-20 in combination with other antiretroviral drugs in treatment-experienced children have been completed, and have demonstrated that the drug is safe and has an additive antiviral effect *[151, 152]*. T-20 was approved in March 2003 for HIV-infected adults and children 6 years of age or older for use in combination with other antiretroviral drugs in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. There are currently insufficient data to recommend use of T-20 for initial therapy of HIV infection in children.

RECOMMENDATIONS ON ANTIRETROVIRAL REGIMENS FOR INITIAL THERAPY (Table 11)

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. 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;
- Incidence and types of drug toxicity with the regimen;
- Availability and palatability of formulations appropriate for pediatric use;
- 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 three types of regimens based on drug class: protease inhibitor-based (2 NRTIs plus a protease inhibitor); NNRTI-based (2 NRTIs plus an NNRTI); and NRTI-based (3 NRTI drugs). Each class-based regimen has advantages and disadvantages. Protease inhibitor-based regimens, while highly potent, have a high pill burden and palatability challenges in children (**Table 10**). NNRTI-based regimens are palatable and effective, but a low genetic barrier to resistance leads to rapid development of drug resistance mutations when therapy does not fully suppress viral replication, and there is cross-resistance among members of this drug class (**Table 9**). Triple NRTI-based regimens, while sparing of other drug classes, may have lower potency than other regimens (**Table 8**). As discussed earlier, within each drug class, some drugs may be preferred over other drugs for treatment of children, based on: the extent of pediatric experience; drug formulation, including taste and volume of syrups and pill size and number; storage and food requirements; and short- and long-term toxicity.

Based on clinical, immunological, and virological data from clinical trials in adults and children, antiretroviral drug regimens are listed as:

- Strongly Recommended,
- Alternative Recommendation,
- Use in Special Circumstances,
- Not Recommended, or
- Insufficient Data to Recommend.

STRONGLY RECOMMENDED REGIMENS FOR INITIAL THERAPY OF CHILDREN (Table 11)

Based on clinical trials in infected adults and children, the antiretroviral regimens that are Strongly Recommended for initial therapy in children include the combination of 2 NRTIs plus one of the Strongly Recommended protease inhibitors, or the combination of 2 NRTIs plus the NNRTI efavirenz for children over age 3 years or nevirapine for children under age 3 years or who cannot take capsules. The choice of dual NRTI was previously discussed.

Protease Inhibitor-Based Strongly Recommended Regimens

Lopinavir/ritonavir, nelfinavir and ritonavir are the Strongly Recommended protease inhibitors for initial therapy of children due to the availability of pediatric formulations, experience in pediatric populations, and relatively low rates of toxicity.

Lopinavir/ritonavir liquid formulation in combination with 2 NRTIs was studied in 100 antiretroviral-naïve (N=44) and experienced (N=56) children in a phase I/II trial *[153]*. The regimen was well tolerated, with only one child permanently discontinuing the study due to a drug-related adverse event. Overall, the mean increase in $CD4^+$ cell count was 404 cells/mm^3 and 79% of children had HIV RNA levels <400 copies/mL after 48 weeks; response was best in the antiretroviral-naïve children, with 88% having HIV RNA <400 copies/mL at 48 weeks.

Nelfinavir and ritonavir-based regimens were studied in antiretroviral-experienced children in PACTG 377; virologic response was similar for both protease inhibitors, with 44-55% of children achieving HIV RNA levels <400 copies/mL at 24 weeks *[154]*. While a higher proportion (63%) of children receiving a 4-drug regimen (d4T/3TC/nevirapine/nelfinavir) had virologic suppression, the study was not designed to evaluate use of these regimens as initial therapy in treatment-naïve children and the number of children studied was limited.

In a small study of nelfinavir with 2 NRTIs in antiretroviral-naïve children, 69% of children had HIV RNA <500 copies/mL after 1 year of therapy *[155]*. Similarly, the PENTA 5 trial, which compared the dual NRTI combinations of ZDV/3TC and 3TC/ABC with or without nelfinavir in antiretroviral naïve children, viral suppression to <400 copies/mL at 24 and 48 weeks was observed with nelfinavir-containing regimens in 68% and 56%, respectively, and to <50 copies/mL in 57% and 48% *[125]*. Adverse effects attributed to nelfinavir were infrequent except for diarrhea. Although the nelfinavir tablets were well tolerated in this trial, the powder was not, and most children switched to crushed tablets. Additionally, the optimal dose for nelfinavir in younger children has not been well defined, and higher doses of nelfinavir are needed to achieve adequate drug levels in infants than older children.

Ritonavir has also been studied in a clinical trial of antiretroviral-experienced, protease inhibitor-naïve children, PACTG 338; drug combinations that included ritonavir were more effective than therapy with 2 NRTI antiretroviral drugs alone in reducing viral load to undetectable levels *[93, 95]*. Additionally, the combination of 2 NRTIs with ritonavir was significantly more effective than use of a single NRTI and ritonavir in reducing viral load to undetectable levels and increasing CD4 lymphocyte percentage after both 24 and 48 weeks of treatment. At 48 weeks, 42% of children receiving ritonavir and 2 NRTIs had HIV RNA <400 copies/mL. However, the liquid formulation of ritonavir has poor palatability, and significant gastrointestinal intolerance (nausea and vomiting) may be a barrier to use of this drug in children.

NNRTI-Based Strongly Recommended Regimens

Efavirenz, in combination with 2 NRTIs with or without nelfinavir, is the Strongly Recommended NNRTI for initial therapy of children over age 3 years who can take capsules, based on clinical trial experience in children and because higher rates of toxicity have been observed in clinical trials in adults with nevirapine (see **data on nevirapine in**

Recommended as Alternative section, **NNRTI-Based Alternative Regimens**); nevirapine is the Strongly Recommended NNRTI for initial therapy of children under age 3 years or who cannot take capsules.

In a pediatric clinical trial, efavirenz in combination with one or two NRTIs and the protease inhibitor nelfinavir reduced viral load to <400 copies/mL in 76% of treated children and to <50 copies/mL in 63%; the regimen was well-tolerated, and the virologic response was sustained through 48 weeks *[134]*. In clinical trials in HIV-infected adults, a protease inhibitor-sparing regimen of efavirenz in combination with ZDV and 3TC was associated with an excellent virologic response, with 70% of treated individuals having HIV RNA <400 copies/mL at 48 weeks *[135]*. However, because efavirenz is only available in a capsule and nevirapine is available in a liquid formulation, nevirapine is the Strongly Recommended NNRTI for children who require a liquid formulation or who are under age 3 years.

RECOMMENDED AS ALTERNATIVES FOR INITIAL THERAPY OF CHILDREN (Table 11)

Antiretroviral regimens Recommended as Alternatives for initial therapy include the combination of 2 NRTIs with the protease inhibitors indinavir or amprenavir (the latter only for children over 4 years of age); the combination of 2 NRTIs with nevirapine (for children aged 3 years or older); or the triple NRTI combination of ZDV/3TC/ABC. While each of the alternative regimens has demonstrated evidence of virologic suppression in some children, either experience in the pediatric population is more limited than for the Strongly Recommended regimens, the extent and durability of suppression less well defined in children, and/or the efficacy may not outweigh potential adverse effects, such as drug toxicity (i.e., indinavir or ABC).

Protease Inhibitor-Based Alternative Regimens

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 *[139, 156-158]*. There is less pediatric experience with amprenavir than the other protease inhibitors, and the liquid formulation cannot be administered to children under age 4 years due to the high concentration of propylene glycol and vitamin E in the liquid preparation. Thus, initial HAART regimens containing either of these protease inhibitors are viewed as Alternative as opposed to Strongly Recommended regimens.

NNRTI-Based Alternative Regimens

Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine, with some studies showing more virologic failures with nevirapine and others showing equivalent efficacy of the two drugs *[159-161]*. No comparative trials of nevirapine and efavirenz have been conducted in children.

In a large nonrandomized study in Italy (I.Co.N.A. study), virologic failure (HIV RNA >500 copies/mL) was observed in 66% of adults initiating therapy with a nevirapine-based regimen compared to 34% of those initiating therapy with an efavirenz-based regimen *[159]*. A randomized clinical trial, the 2NN study, compared d4T/3TC combined with either nevirapine given once daily; nevirapine twice daily; efavirenz once daily; or once daily nevirapine and efavirenz together *[161]*. Although nevirapine and efavirenz had comparable virologic efficacy (HIV RNA <50 copies/mL at 48 weeks in 64-65% of those on nevirapine versus 68% of those receiving efavirenz), serious hepatobiliary toxicity was more frequent in the nevirapine than efavirenz arm (clinical toxicity in 2-3% of those on nevirapine compared to 0.5% of those on efavirenz; laboratory toxicity in 8-13% of those on nevirapine compared to 5% on efavirenz); the dual nevirapine/efavirenz regimen was associated with both higher treatment failure and increased toxicity. Other studies in adults have indicated potential increased risk for hepatic toxicity with nevirapine compared to efavirenz-based regimens *[162]*. Because of the potential for higher rates of hepatic toxicity, nevirapine-based regimens are viewed as an Alternative rather than a Strongly Recommended regimen, except for children under age 3 years or who require a liquid formulation.

NRTI-Based Alternative Regimens

In a randomized trial, the triple NRTI combination of ZDV/3TC/ABC 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 comparison arm of ZDV/3TC and indinavir *[163]*. 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 *[164]*. Data on the efficacy of triple NRTI regimens for treatment of antiretroviral naïve children is limited; in small observational studies, response rates of 47-50% have been reported *[165, 166]*. The triple-NRTI regimen spares the initial use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors and can be administered twice a day in children, which may facilitate adherence *[124, 167]*. However, a clinical trial (ACTG 5095) in antiretroviral naïve adults that compared initial therapy with ABC/ZDV/3TC, efavirenz/ZDV/3TC, or efavirenz/ZDV/3TC/ABC 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 ABC/ZDV/3TC had HIV RNA <200 copies/mL compared to 89% of patients receiving efavirenz-based regimens *[168, 169]*. Therefore, because of the uncertain long-term durability of viral load suppression with a regimen comprised of three drugs of a single class (NRTIs), disappointing results in the treatment of antiretroviral-experienced children, the recent adult data suggesting an inferior virologic response with ABC/ZDV/3TC compared to efavirenz-based regimens, and the potentially life-threatening hypersensitivity syndrome associated with ABC *[126, 127]* this drug combination is Recommended as an Alternative for initial therapy.

USE IN SPECIAL CIRCUMSTANCES FOR INITIAL THERAPY OF CHILDREN (Table 11)

Dual NRTI therapy alone is recommended for initial therapy only in Special Circumstances. Use of a regimen consisting of 2 NRTIs alone may be considered when the health care provider or guardian/ patient has concerns regarding the feasibility of adherence to a more complex drug regimen. It is important to note that drug regimens that do not result in sustained viral suppression, such as a dual NRTI regimen, may result in the development of viral resistance to the drugs being used and cross-resistance to other drugs within the same drug class. Thus, a dual NRTI regimen would be chosen for initial therapy only under very limited circumstances.

NOT RECOMMENDED FOR INITIAL THERAPY OF CHILDREN (Table 11)

Antiretroviral regimens that are Not Recommended for treatment include monotherapy, certain dual NRTI combinations (ZDV and d4T; and ddC and ddI, d4T or 3TC), and saquinavir-SGC or saquinavir-HGC as sole protease inhibitors (**Table 11**). These combinations are Not Recommended either because of pharmacological antagonism, potential overlapping toxicities, or inferior virologic response. As noted earlier, the appropriate pediatric dose of saquinavir-SGC has not been defined, and boosting with a second protease inhibitor (nelfinavir or low-dose ritonavir) is required to produce efficacious plasma drug levels; however, there are currently insufficient data to determine appropriate dosage of such combinations in children *[148, 150]*.

INSUFFICIENT DATA FOR RECOMMENDATION FOR INITIAL THERAPY FOR CHILDREN (Table 11)

There are Insufficient Data to Recommend a number of different antiretroviral drug regimens for initial therapy of antiretroviral naïve children. These include: regimens containing the NNRTI delavirdine, which has not been studied in HIV-infected children and is not available in a liquid formulation; dual protease inhibitor-based regimens (with the exception of lopinavir-ritonavir, a co-formulated preparation), because there are only limited data on appropriate dosing and safety of such regimens; regimens containing agents from 3 drug classes (e.g., NRTI plus NNRTI plus a protease inhibitor), with the exception of efavirenz plus nelfinavir and 1 or 2 NRTIs, which has been shown to be effective in HIV-infected children *[132]*; or regimens containing tenofovir, enfuvirtide, FTC, atazanavir, or fosamprenavir drugs for which pediatric pharmacokinetic and safety data are not currently available and which are not available in liquid formulations.

ISSUES REGARDING ANTIRETROVIRAL DOSING IN NEONATES

Data regarding the appropriate dosing of antiretroviral drugs in neonates are limited; ZDV is the best-studied antiretroviral drug in this age group. The recommended ZDV dosage for infants was derived from pharmacokinetics studies performed in full-term infants *[170]*. Because ZDV is primarily cleared through hepatic metabolism (i.e., glucuronidation), which is immature in neonates, the half-life and clearance of ZDV are prolonged in neonates compared with older infants, thus requiring adjustments in dosing. The dosing regimen for full-term neonates is 2 mg/kg orally every 6 hours or 1.5 mg/kg intravenously every 6 hours.
Premature infants have even greater immaturity in hepatic metabolic function than do full-term infants, and further prolongation in clearance has been documented in very premature infants (i.e., those born before 34 weeks' gestation) *[171, 172]*. Results from a phase I clinical trial of ZDV in premature infants (PACTG 331) demonstrated that the dosing schedule for premature infants should be 1.5 mg/kg intravenously, or 2.0 mg/kg orally, every 12 hours, which is increased to every 8 hours at 2 weeks of age if $\geq$30 weeks' gestation at birth, or at 4 weeks of age if <30 weeks' gestation at birth *[172]*.

The safety and pharmacokinetics of 3TC administered alone or in combination with ZDV in pregnant women and administered for 1 week to their newborns have been evaluated *[173, 174]*. Clearance was prolonged in these infants. Based on data from this study, the dose recommended for use in newborns (2 mg/kg orally twice daily) is half the dose recommended in older children (4 mg/kg twice daily). Systemic exposure to ZDV administered as a 4 mg/kg twice daily regimen was similar to that reported with the standard neonatal ZDV regimen of 2 mg/kg every 6 hours in a small study evaluating use of ZDV/3TC for prophylaxis of perinatal HIV transmission in 16 HIV-exposed infants in South Africa *[174]*; however, data comparing efficacy in HIV-infected children of twice daily to standard four times a day ZDV are not available. No data are available regarding 3TC pharmacokinetics among infants aged 2 to 6 weeks, and the exact age at which 3TC clearance begins to approximate that in older children is not known. However, glomerular filtration approximately doubles during the first 4 weeks of life and secretion capacity of the kidney reaches adult values at about 30 weeks of life; based on these data, the dose of 3TC in a phase II study, PACTG protocol 356, is increased to 4 mg/kg twice daily for infected children over 4 weeks of age.

The safety and pharmacokinetics of ddI administered to pregnant women and their neonates have been evaluated in PACTG protocol 249 *[175]*. A single oral dose of 60 mg/m^2 at 12–24 hours of age and age 6 weeks was studied in the neonates. The pharmacokinetics of ddI in four neonates were found to be highly variable, and in three of the four neonates, the oral clearance of ddI increased and the terminal half-life decreased from age 1 day to 6 weeks; the mean half-life at day one was 135 minutes versus 68 minutes at 6 weeks. In a multidosing study (PACTG protocol 239) in infected infants, acceptable pharmacokinetics were found with a ddI dose of 50 mg/m^2 every 12 hours for infants aged 90 days or less.

The pharmacokinetics of d4T (1 mg/kg twice daily) and ddI (100 mg/m^2 once daily) were studied in HIV-exposed neonates in Thailand *[176]*. Systemic levels of exposure to d4T and peak concentrations were comparable to that seen in older children, suggesting that the standard pediatric d4T dose was appropriate for neonates. Levels of exposure to ddI in neonates at the dose of 100 mg/m^2 once daily were modestly higher than seen in older children. PACTG 332 was a single-dose pharmacokinetic study of d4T (1 mg/kg) given to neonates at age 6 days and 42 days. Oral clearance was lower and half-life longer at age 6 than 42 days, but the systemic exposure (area under the curve, AUC) and peak levels were similar at both times *[177]*.

Preliminary data are available on the pharmacokinetics of ABC in neonates from PACTG protocol 321 *[178]*. A single 2 mg/kg oral ABC dose was administered to neonates less than 30 days of age. Clearance was found to be much less than observed in older children and the half-life significantly longer. The 2 mg/kg dose in the neonate yielded ABC concentrations similar to or greater than the concentration in older children at the recommended dose of 8 mg/kg; in the phase II study PACTG protocol 356, ABC dosing for infants over 30 days of age is 8 mg/kg twice daily.

NVP administration to HIV-infected pregnant women during labor and as a single dose of 2 mg/kg orally to their newborns at age 2 to 3 days has been studied in a phase I trial *[179]*. The half-life of NVP was prolonged in neonates compared with that in older children, indicating that some modification of

NVP dosage is required for administration to neonates. The single dose at 48–72 hours in infants born to women who had received NVP during labor maintained NVP concentrations above the desired 100 ng/mL (10 times the IC_{50}) in the infant through 7 days of age. This regimen of a single dose NVP during labor and a single dose to the infant age 2 to 3 days was subsequently shown in a phase III clinical trial in Uganda to significantly reduce the risk of perinatal transmission *[133]*.

Information on the NVP dose for treatment of infected neonates (as opposed to prophylaxis of transmission) is less studied. The limited single dose 2 mg/kg NVP pharmacokinetic data in the neonate showed that elimination is lower than in older children but comparable to that in adults *[179]*. However, multidose NVP pharmacokinetics have been evaluated in children as young as 2 months; in the youngest children, clearance was lower than in older children but greater than in adults, suggesting rapid maturation of NVP metabolism during the first 2 months of life *[180]*. A study of pharmacokinetics of the single NVP dose in 10 infants born to infected mothers who have received multiple NVP doses (as opposed to a single dose) during pregnancy indicated that a single infant NVP dose of 2 mg/kg orally at age 48–72 hours did not maintain NVP concentrations above the desired 100 ng/mL through age 7 days in 4 of 10 infants, suggesting possible *in utero* induction of NVP metabolic enzymes in the fetal liver, and that NVP may need to be given more than once during the first week of life to maintain virucidal levels when the mother has received NVP treatment during pregnancy *[181]*. The NVP dose for infected infants aged 15 days to 3 months is under study in a phase II clinical trial, PACTG protocol 356. For infants aged 15 to 29 days, the regimen is 5 mg/kg orally once daily for 14 days, followed by 120 mg/m^2 orally every 12 hours for 14 days, followed by 200 mg/mm^2 orally every 12 hours.

Nelfinavir, ritonavir, saquinavir, or indinavir in combination with ZDV/3TC have been studied in phase I studies in pregnant HIV-infected women; transplacental passage of the drugs was minimal. Additionally, in a study of protease inhibitor concentrations in cord blood from 68 women who received antenatal protease inhibitor therapy, the concentration of the protease inhibitor was below the assay limit of detection in most samples, including all samples from women receiving indinavir and saquinavir, or was present at very low levels *[182]*. In the phase I pregnancy studies of nelfinavir and ritonavir, administration of the protease inhibitor in combination with ZDV/3TC for 6 weeks to the neonate was also studied. During the first year of life, nelfinavir concentrations have been observed to be highly variable, and dose requirements appear to be much higher than in older children and adults to obtain similar drug exposures *[112, 183, 184]*. In the phase I perinatal study, PACTG protocol 353, administration of NFV in a dose of 10 mg/kg three times daily to the neonate for the first 6 weeks of life produced inadequate NFV levels, and a dose of 40 mg/kg twice daily produced adequate levels in 72% of infants, but 28% had unsatisfactory levels *[185]*. In the phase II trial PACTG protocol 356, preliminary data on the pharmacokinetics of NFV given as 30 mg/kg three times daily in infants 15 days or older indicated that this produced inadequate drug levels, and a dose of 55–65 mg/kg twice daily is currently under study in this age group; infants over 3 months receive a dose of 30 mg/kg three times daily. Similarly, a study of ritonavir in neonates (PACTG 345) demonstrated high variability in ritonavir concentrations among infants and lower concentration and higher clearance than in older children and adults, with doses of 350 and 450 mg/m^2 producing inadequate drug levels in a substantial proportion of infants *[105]*. Data on dosing of the other protease inhibitors in neonates is not available at this time.

CHANGING ANTIRETROVIRAL THERAPY

When to Change Antiretroviral Therapy

Patients taking antiretroviral therapy require careful monitoring for medication adherence, virologic, immunologic, and clinical response, and medication intolerance and toxicity. The following are the major indications warranting the review and possible change in antiretroviral therapy:

a. Failure of the current regimen with evidence of disease progression based on virologic, immunologic, or clinical parameters (**Table 12**);
b. Toxicity or intolerance to the current regimen; and/or
c. Consideration of new data demonstrating that a drug or regimen is superior to the current regimen.

When treatment fails or provides only sub-optimal response, clinicians working with patients and their families need to assess the likely contribution of adherence problems to the failure of the current regimen. Even small lapses in adherence can lead to antiretroviral treatment failure. Directly observed therapy, including inpatient hospitalization, may be necessary to distinguish between inadequate adherence and medication failure.

Issues regarding adherence should be addressed to increase the likelihood of a successful outcome when initiating any new regimen. Intensive family education, training in the administration of prescribed medications, and discussion of the importance of adherence to the drug regimen should be completed before initiation of new treatment. In addition, 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 and to monitor adherence, tolerance, and virologic response to the new regimen.

Virologic Considerations for Changing Therapy

The general virologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons. Because HIV RNA monitoring is critical for the management of infected children, Working Group members used the available data, and clinical experience when definitive data were not available, to make the following recommendations. These recommendations may require modification as new information becomes available.

Ideally, antiretroviral therapy should maximally suppress viral replication to undetectable levels using HIV RNA assays. This may not always be achievable in HIV-infected children. Perinatally infected children generally have high HIV RNA levels, and clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels. However, failure to maximally suppress replication may be associated with increased probability of viral mutations and the emergence of drug resistance. Consideration of the implications of changing regimens and the choice of new drugs should include an acknowledgment of the potential for limiting the patient's future options for potent therapy.

Consensus recommendations have been developed using plasma HIV RNA measurements to guide changes in antiretroviral therapy for HIV-infected adults *[5]*. Because HIV RNA levels in infants who are perinatally infected are high compared with levels observed when therapy is initiated in most infected adults, the initial virologic response of infected infants and young children to initiation of antiretroviral therapy may take longer than observed in adults. In addition, suppression of HIV RNA to undetectable levels may be achieved less often than has been reported for infected adults despite potent combination therapy with 2 NRTIs and a PI. Therefore, virologic indications for changing therapy in infected children differ slightly from those recommended for infected adults. Adult guidelines should be followed for infected adolescents.

Virologic response should be assessed within 4 weeks after initiating or changing therapy. However, the time required to achieve maximal virologic response to therapy may vary depending on the specific baseline HIV RNA value at the time of starting therapy. After a maximal virologic response is achieved, HIV RNA levels should be measured at least every 3 months to monitor continued response to therapy. At least two measurements (taken 1 week apart) should be performed before considering a change in therapy. Resistance testing is recommended in the setting of persistent or increasing HIV RNA levels.

The following situations may indicate a need for change in therapy in infected children. It should be emphasized that partial non-adherence can explain each of the scenarios listed below and must be addressed prior to making any medication changes.

- **Less than a minimally acceptable virologic response after 8–12 weeks of therapy.** For children receiving aggressive antiretroviral therapy, such a response is defined as a less than tenfold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels.
- **HIV RNA not suppressed to undetectable levels after 4–6 months of antiretroviral therapy.** Although suppression of HIV RNA to undetectable levels and maintenance for prolonged periods is desirable, some data indicate that suppression is not always achievable. In addition, the number of alternative therapeutic regimens for children is limited. 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 to 2.0 $\log_{10}$ fall in HIV RNA copy number, even if RNA remains detectable at low levels.

- **Repeated detection of HIV RNA in children who initially had undetectable levels in response to antiretroviral therapy.** 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). The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations.
- **A reproducible increase in HIV RNA copy number among children who have had a substantial HIV RNA response but still have low levels of detectable HIV RNA.** Such an increase would warrant a change in therapy if, after achieving a virologic nadir, a greater than threefold (>0.5 $\log_{10}$) increase in copy number is observed in children aged $\geq$2 years. Because of the greater biologic variability in RNA in young children, a change in therapy is warranted when a greater than fivefold (>0.7 $\log_{10}$) increase is observed for children aged <2 years.

Immunologic Considerations for Changing Therapy

$CD4^+$ T cell count and percentage are independent predictors of disease progression and mortality in HIV-infected children *[51, 52]*. The association of HIV RNA and $CD4^+$ T cell percentage with long-term mortality risk in HIV-infected children has been evaluated; for each absolute decline of five percentiles in $CD4^+$ T cell percentage at baseline or during follow up, the mortality risk ratio increased by 1.3 (95% CI=1.2–1.5), independent of the child's HIV RNA level *[51]*. For children with $CD4^+$ T cell percentages of <15% (i.e., those in immune category 3), prognosis also was correlated with the degree of depression of $CD4^+$ T cell percentage (i.e., life expectancy was less for children with $CD4^+$ T cell percentages of <5% compared with children with $CD4^+$ T cell percentages of 10%–14%) (**Table 3**).

Before considering changing antiretroviral therapy because of a decline in $CD4^+$ T cell values, a minimum of one repeated measurement of $CD4^+$ T cell values should be obtained at least 1 week after the initial test. The following immunologic indications may warrant a change in antiretroviral therapy for HIV-infected children:

- Change in immune classification (**Table 1**). However, minimal changes in $CD4^+$ T cell percentile that may result in a change in immune category (i.e., from 26% to 24% or from 16% to 14%) may not be as concerning as a rapid substantial change in $CD4^+$ T cell percentile within the same immune category (i.e., a decrease from 35% to 25%).
- For children with $CD4^+$ T cell percentages of <15% (i.e., those in immune category 3), a persistent decline of 5 percentiles or more in $CD4^+$ T cell percentage (i.e., from 15% to 10% or from 10% to 5%).
- A rapid and substantial decrease in absolute $CD4^+$ T cell count (i.e., a >30% decline in <6 months).

Potent antiretroviral therapy usually increases $CD4^+$ T cell values. Failure of a regimen to improve $CD4^+$ T cell values for patients in immune category 3 should prompt review of the available treatment options and possible change in the antiretroviral regimen.

Clinical Considerations for Changing Therapy

The occurrence of certain clinical events while receiving antiretroviral therapy is evidence of HIV disease progression and/or a poor prognosis for infants and children. The following clinical criteria warrant consideration of a change in antiretroviral therapy:

- Progressive neurodevelopmental deterioration (i.e., 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). In such cases, the new treatment regimen optimally should include at least one antiretroviral drug with substantial central nervous system penetration (i.e., ZDV or NVP, which have cerebrospinal fluid/plasma ratios >0.5).
- Growth failure (i.e., persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation).
- Disease progression (i.e., advancement from one pediatric clinical category to another; see **Table 2**). Prognosis is poorer as patients' progress to more advanced clinical categories. However, in patients with stable immunologic and virologic parameters, progression from one clinical category to another (i.e., from clinical category A to category B) may not represent an indication to change therapy. For

example, development of new opportunistic infections, particularly in patients who had severe immunosuppression at the time therapy was initiated, may not reflect a failure of antiretroviral therapy but persistence of immunologic dysfunction despite adequate antiviral response. Thus, in patients whose disease progression is not associated with neurologic deterioration or growth failure, virologic and immunologic parameters should be considered when deciding whether to change therapy.

Choice of a New Antiretroviral Regimen

The choice of a new antiretroviral regimen is dictated by the indications that warranted the change in therapy (e.g. toxicity/intolerance vs. drug resistance vs. poor adherence) and the available alternative antiretroviral agents. Although the efficacy of different combination antiretroviral regimens in children probably can be extrapolated from clinical trial data obtained for adults, data are limited regarding the pharmacokinetics, appropriate dosing, and short- and long-term safety of various combinations in infected children. A decision to change therapy and the proposed new regimen to be chosen should partly take into account the impact of the changes on future treatment options.

The following principles should be followed when choosing a new antiretroviral regimen in children who have received prior treatment.

- When therapy is changed because of toxicity or intolerance, agents with different toxicity and side-effect profiles should be chosen, when possible. Health care providers 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 multidrug regimen—and in certain circumstances, dose reduction—are permissible options. Only reduce antiretroviral drug doses to the lower end of the therapeutic range when 1) an effective dosing range is known, 2) drug toxicity is caused by a higher than acceptable drug exposure, and 3) drug levels can be monitored to ensure that plasma concentrations stay within the therapeutic range. While adequacy of antiretroviral activity should be confirmed by monitoring of HIV RNA levels in the period immediately following the regimen change, subtherapeutic dosing may not manifest with sudden increase in viral load, but rather may result in shortened duration of benefit.
- Before changing therapy because of treatment failure (**Table 12**), adherence to therapy should be assessed to determine what role it played as a potential cause of treatment failure.
- In addition to poor adherence, inadequate drug exposure can occur with inadequate absorption or rapid drug metabolism. Drug exposure may be enhanced or reduced by administering medications with food. These factors should also be considered as potential contributing factors when a regimen fails. Drug interactions can alter drug metabolism, and all concomitant medications, including over the counter medications and nutritional supplements, should be reviewed to understand whether they might play a role in regimen failure and to make sure appropriate medications and doses are chosen for any new regimens.
- If the patient is adherent to the prescribed drug regimen, assume the development of drug resistance to one or more of the medications in the regimen and perform resistance testing (genotypic or phenotypic) before discontinuing the regimen or initiating a new regimen. (See **Antiretroviral Drug Resistance Testing**). If possible, change at least two drugs to new antiretroviral agents. A change in one drug or addition of a single drug to a failing regimen is suboptimal. Whenever possible, the new regimen should contain at least 3 medications with combinations guided by the same decision process used to develop the initial regimen (**Table 11**). The potential for cross-resistance between antiretroviral drugs should be considered.
- A change to a new regimen, especially one containing PIs or NNRTIs, must include a discussion of treatment adherence issues by the health care provider with the patient, when age-appropriate, and caregivers of the infected child. The health care provider must recognize that certain medications are difficult to take in combination because of exacting and often conflicting requirements with respect to whether they can be taken with food and other antiretrovirals. Palatability, pill size, pill number and dosing frequency are part of the considerations in choice of new regimen and should be discussed with the child, when appropriate, and the child's caregivers.
- When considering changing to a new regimen, all other medications taken by the patient should be reviewed for possible drug interactions.

- For patients requiring a change of therapy for treatment failure but without treatment options using currently approved drugs, referral to a pediatric HIV specialist for inclusion into a clinical trial should be considered.
- Some studies, primarily in adults, have demonstrated that some patients who are maintained on HAART (primarily protease inhibitor-based regimens) may maintain immunologic (e.g. CD4+ cell count) and clinical benefit for up to 3 years despite detectable viral replication *[186-189]*. Therefore, in patients who have persistent improvement in CD4+ cell count despite detectable viremia, some clinicians would consider continuation of antiretroviral therapy as long as immunologic benefit was observed. However, sequential development of resistance mutation is noted with increasing time since virologic failure *[108, 190]*. If appropriate alternative drugs become available, it is usually preferable to change therapy before higher levels of resistance or broad cross-resistance develops. Optimizing a treatment regimen may best be accomplished through consultation with a pediatric HIV specialist.
- When changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered. Frank discussions of the relative benefits (reduced viral fitness, continued clinical benefit despite resistance, etc.) and burdens of continued antiretroviral therapy should occur. Decisions to continue or discontinue antiretroviral therapy should be made collaboratively with patients, families and health care providers and should be consistent with the patient's/family's stated values and goals for care. There may be clinical and immunologic benefit in continuing a "failing" regimen because of the decrease in viral fitness associated with continuing therapy despite multiresistant virus and increasing viral load *[191, 192]*.
- The creation of an effective and sustainable therapeutic regimen may be limited by the availability of potent and/or tolerable therapeutic agents. When deciding whether to change therapy and the contents of a regimen, the clinician should consider the potential availability and future use of newer therapeutic agents that may be in clinical development. Information concerning potential trials can be found at **http://aidsinfo.nih.gov/clinical_trials** or through discussions with a pediatric HIV expert.

Detailed information regarding issues associated with specific drug choices for changing a failing regimen and potential cross-resistance between various antiretroviral drugs is available elsewhere *[5]*. Because these issues are similar for all HIV-infected persons (regardless of age), they are not addressed specifically in this document.

Antiretroviral Drug Resistance Testing

The optimal goal of antiretroviral therapy is to reduce plasma HIV RNA to below detection of the most sensitive assay available (<50 copies/mL). Accomplishing this level of viral suppression, while not always possible in perinatally infected infants and children, will reduce the likelihood that genotypic (GT)/phenotypic (PT) resistance will emerge.

Several GT assays are available for detecting specific HIV genetic variants (mutations). They are based on amplification procedures and can usually detect mutations in plasma samples with more than 1,000 copies/mL of HIV RNA *[193]*. A compilation of the most common HIV-1 mutations selected by currently available antiretroviral agents is on the Internet at **http://hiv-web.lanl.gov** or **http://hivdb.stanford.edu**.

PT assays directly measure the ability of the viral isolate to grow in the presence of a drug and measure the 50% or 90% inhibitory concentrations of a drug against the virus *in vitro*, compared to a laboratory strain of wild type virus. The result is expressed as a "fold-change" in susceptibility above a particular cut-off level, below which the virus is assumed to be drug sensitive. These assays have historically been more complex than GT assays but are now available from commercial laboratories.

A method for predicting PT based on the GT is also available. This method matches 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 based on the mean of all the individual samples matching the patient's genotype. The result is expressed as a fold-change. In this assay, both the GT and predicted PT are contained in the test report.

Results of clinical trials with laboratory endpoints in adults have indicated that using genotypic or phenotypic testing to help guide changes in antiretroviral therapy results in a significantly

greater, short term, virologic response compared to clinical judgment alone *[194, 195]*. Although results of similar trials in children are not available, most pediatric experts do not think viral replication in the face of resistance differs between children and adults.

Therefore, the Working Group recommends the use of resistance assays (either GT or PT) when considering changing antiretroviral therapy because of virologic failure. While there are insufficient pediatric data to recommend use of one type of resistance assay over the other, an individual patient should have one assay used consistently. In children who have complex antiretroviral treatment histories, the use of both assay types (GT and PT) may provide complimentary information that could prove useful in selecting a new regimen.

Resistance assays should be obtained when patients are still on the failing regimen and have a viral load of greater than 1,000 copies/mL. If no resistance to currently used antiretroviral agents is detected in the face of virologic failure, it is likely that the patient is not adhering to the current regimen, and adherence issues should be addressed.

Infected infants born to ARV-experienced women may become infected with resistant maternal viral strains. In one early study, only the wild type virus was found in infected infants born to mothers who had a mixed viral population of wild type and low-level zidovudine resistant strains *[196]*. However, antiretroviral drug resistance in newly infected infants may become more prevalent over time; 12% of HIV-infected infants born in New York in 1998 and 1999 and evaluated for drug resistance within the first 6 months of life had provirus containing resistance mutations *[117]*. While there are no definitive data that demonstrate that resistance testing correlates with greater success of initial antiretroviral therapy in newly diagnosed infants under age 12 months, the Working Group recommends consideration of resistance testing prior to initiation of therapy in this setting.

The presence of viral resistance to a particular drug suggests that this drug is unlikely to suppress viral replication. However, the absence of resistance to a drug does not insure that its use will be successful, particularly if it shares cross-resistance with drugs previously used. GT or PT assays will detect resistance of the major viral species present, but will not detect resistance in minor viral species constituting less than 10-20% of the circulating viral population. Thus, drug resistant virus could still be present at levels below detection with the current assays if resistance developed to an antiretroviral drug previously used, but not part of the child's current regimen. Inability to detect virus is due to the loss of growth advantage of the resistant virus after a specific drug is discontinued. The history of past use of antiretroviral agents is therefore essential in making decisions regarding the choice of new agents for patients with virologic failure. Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting an ARV regimen in infants or changing an antiretroviral regimen in children.

MANAGING COMPLICATIONS OF HIV INFECTION

The Pediatric Antiretroviral Treatment Guidelines now include the supplements "**Managing Complications of HIV Infection**" and "**Adverse Effects in HIV-Infected Children on Antiretroviral Therapy**". These supplements contain guidelines for special management issues in pediatric HIV infection, including pain management and nutrition, 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. Earlier versions of these documents were previously included in a companion document to the **Pediatric Antiretroviral Treatment Guidelines**; this companion document was published as a supplement in *Pediatrics* in 1998. The Working Group will update the "Managing Complications" supplement to the DHHS *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* with additional sections on management and adverse drug events as needed, or will refer to other pediatric HIV management consensus documents.

The USPHS and the IDSA jointly developed and published guidelines for the prevention of opportunistic infections in both children and adults with HIV *[197]*. These guidelines are available online at the *AIDSinfo* Web site (see the ***2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus***). Separate

guidelines for the treatment of opportunistic infections in HIV-exposed and infected children have been developed, and will be published and available online in the near future.

CONCLUSION

The Working Group has attempted to provide information specific to the use of antiretroviral drugs in infants, children, and adolescents while not duplicating the information available in antiretroviral recommendations for adults *[5]*. Documents addressing recommendations for adults should be reviewed for basic information regarding disease pathogenesis and drug interactions. Although the general principles of therapy are the same for HIV-infected adults, adolescents, children, and infants, treatment of infection in pediatric patients requires an understanding of the unique aspects of HIV infection in children. Clinical trials of antiretroviral agents in HIV-infected children and the development of drug formulations appropriate for administration to children have often been delayed until after clinical trials in infected adults have been completed and/or the drug has been approved for use among infected adults. However, despite these delays, the paucity of pediatric-specific data cannot further deter the development of rational and reasonable pediatric treatment guidelines while studies in children are being undertaken. To maximize therapeutic options for HIV-infected pediatric patients throughout the course of their infection, drug formularies should facilitate the use of all FDA-approved antiretroviral agents as treatment options for children.

Additionally, the conduct of clinical trials to define the pharmacokinetics, safety, and effectiveness in ameliorating the pediatric-specific manifestations of HIV infection of current and new antiretroviral agents is a priority; studies of new drugs should be conducted coincident with or soon after initial studies have been completed in adults. The Working Group will revise these guidelines as new data regarding antiretroviral therapy for infected infants, children, and adolescents become available.

Table 1. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific $CD4^+$ T Cell Count and Percentage*

	< 12 mos		1–5 yrs		6–12 yrs	
Immune category	**No./mm^3**	**(%)**	**No./mm^3**	**(%)**	**No./mm^3**	**(%)**
Category 1: No suppression	≥ 1,500	(≥25%)	≥ 1,000	(≥25%)	≥500	(≥25 %)
Category 2: Moderate suppression	750–1,499	(15%–24%)	500–999	(15%–24%)	200–499	(15%–24%)
Category 3: Severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

* Modified from: CDC. 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.

Table 2: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories*

Category N: Not Symptomatic

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

Category A: Mildly Symptomatic

Children with **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)

Category C: Severely Symptomatic

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

* 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.

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

	CD4 Percentage				Log_{10} HIV RNA Copy Number		
Age	**10%**	**20%**	**30%**	**40%**	**6.0**	**5.0**	**4.0**
Percent Developing AIDS (95% Confidence Interval)							
6 Months	51	31	20	16	24	14	11
	(45-57)	(27-35)	(18-23)	(14-17)	(16-27)	(10-16)	(7-16)
1 Year	40	21	13	9.9	21	11	7.8
	(45-57)	(18-23)	(12-14)	(8.5-11.4)	(12-24)	(8-12)	(4.4-12.1)
2 Years	29	12	7.2	5.9	19	8.1	5.3
	(26-31)	(11-14)	(6.4-8.2)	(4.9-7.1)	(8-22)	(6.5-9.3)	(3.2-8.5)
5 Years	15	4.7	3.1	2.9	17	6.0	3.2
	(12-18)	(3.9-5.7)	(2.5-4.0)	(2.1-3.8)	(5-21)	(4.5-8.0)	(2.1-4.9)
10 Years	7.4	2.2	1.8	1.7	16	5.1	2.2
	(5.0-10.8)	(1.6-2.8)	(1.2-3.0)	(1.1-3.1)	(3-20)	(3.0-7.7)	(1.4-3.2)
Percent Mortality (95% Confidence Interval)							
6 Months	30	12	6.4	4.6	9.7	4.1	2.7
	(26-35)	(10-15)	(5.3-7.8)	(3.8-5.5)	(8.1-12.0)	(2.9-5.4)	(0.9-4.1)
1 Year	20	6.8	3.3	2.5	8.8	3.1	1.7
	(18-23)	(5.6-8.4)	(2.8-3.9)	(2.0-3.1)	(7.2-11.0)	(2.4-4.0)	(0.8-2.8)
2 Years	12	3.1	1.5	1.2	8.2	2.5	1.1
	(11-14)	(2.6-3.7)	(1.2-1.9)	(0.9-1.6)	(6.4-10.4)	(1.8-3.1)	(0.6-1.8)
5 Years	4.9	0.9	0.5	0.5	7.8	2.1	0.7
	(3.8-5.9)	(0.7-1.2)	(0.3-0.7)	(0.3-0.7)	(5.9-10.2)	(1.4-2.9)	(0.4-1.0)
10 Years	2.1	0.3	0.2	0.2	7.7	2.0	0.6
	(1.3-3.0)	(0.2-0.5)	(0.1-0.4)	(0.1-0.4)	(5.7-10.0)	(1.2-2.9)	(0.3-0.9)

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

Table 4. 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*

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.

Table 5. Strategies to Improve Adherence with Antiretroviral Medications

Initial Intervention Strategies

- Establish trust and identify mutually acceptable goals for care.
- Obtain explicit agreement on need for treatment and adherence.
- Identify depression, low self-esteem, or drug use that may decrease adherence. Treat prior to starting therapy, 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.
- Identify 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 best-tasting liquid medicine possible.
- Choose drugs with the fewest side effects; inform patient regarding medication side effects; anticipate and treat 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 trying to be >95% adherent 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 or one-on-one counseling for patients with depression or drug use issues that are known to decrease adherence.
- Provide pharmacist-based adherence clinics.
- Consider gastrostomy tube use in selected circumstances.
- Consider a brief period of hospitalization during therapy in selected circumstances of apparent virologic failure to assess adherence and reinforce that medication adherence is fundamental to successful antiretroviral therapy.

Table 6. Indications for Initiation of Antiretroviral Therapy in Children <12 Months of Age Infected with Human Immunodeficiency Virus (HIV) Infection

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; 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 caregivers for the HIV-infected infant before the decision to initiate therapy is made.

Clinical Category		CD4+ Cell Percentage	Plasma HIV RNA Copy Number [1]	Recommendation
Symptomatic (Clinical category A, B, or C)	***OR***	<25% (Immune category 2 or 3)	Any value	Treat
Asymptomatic (Clinical category N)	***AND***	≥25% (Immune category 1)	Any value	Consider Treatment [2]

[1] Plasma HIV RNA levels are higher in HIV-infected infants than older infected children and adults. Because overall HIV RNA levels are high and overlap between infants who have and those who do not have rapid disease progression, HIV RNA levels may be difficult to interpret in infants <12 months of age.

[2] Because HIV infection progresses more rapidly in infants than older children or adults, some experts would treat all HIV-infected infants <6 months or <12 months of age, regardless of clinical, immunologic or virologic parameters.

Table 7. Indications for Initiation of Antiretroviral Therapy in Children ≥1 Year of Age Infected with Human Immunodeficiency Virus (HIV)

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 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.

Clinical Category		$CD4^+$ Cell Percentage		Plasma HIV RNA Copy Number	Recommendation
AIDS (Clinical category C)	***OR***	<15% (Immune Category 3)		Any value	Treat
Mild-Moderate Symptoms (Clinical category A or B)	***OR***	15-25% [1] (Immune Category 2)	**OR**	≥100,000 copies/mL [2]	Consider treatment
Asymptomatic (Clinical category N)	***AND***	>25% (Immune Category 1)	**AND**	<100,000 copies/mL [2]	Many experts would defer therapy and closely monitor clinical, immune, and viral parameters

[1] Many experts would initiate therapy if $CD4^+$ cell percentage is between 15 to 20%, and defer therapy with increased monitoring frequency in children with $CD4^+$ cell percentage 21% to 25%.

[2] There is controversy among pediatric HIV experts regarding the plasma HIV RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV RNA levels were between 50,000 to 100,000 copies/mL.

Table 8: one of two pages

Table 8. Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Combinations for Use in Highly Active Antiretroviral Combination Regimens

	Advantages	Disadvantages
General Issues		
NRTI/NtRTI-Based Regimens	**NRTI Class Advantages:** • Minimal drug-drug interactions • Protease inhibitor and NNRTI-sparing • Only limited cross resistance among NRTIs • Easier to use and adhere to than protease inhibitor-based regimens • One combination is coformulated as single pill for older/larger patients (ZDV/3TC/ABC, Trizivir); low pill burden	**NRTI Class Disadvantages:** • Rare but serious and potentially life-threatening cases of lactic acidosis and hepatic steatosis with all NRTIs/NtRTI • ZDV/3TC/ABC (Trizivir) has inferior virologic response compared to efavirenz-based regimens or to indinavir-based regimens in adults • Use of ZDV/3TC/ABC (Trizivir) coformulation has potential for ABC hypersensitivity reaction
Strongly Recommended Combinations		
ZDV plus 3TC	• Extensive pediatric experience • Coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food	• Bone marrow suppression with ZDV • Single mutation confers 3TC resistance
ZDV plus ddI	• Extensive pediatric experience • Videx EC 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 liquid formulation • Food effect (ddI needs to be taken 1 hour before or 2 hours after food)
d4T plus 3TC	• Moderate pediatric experience • Palatable liquid formulations • Can give with food • Zerit XR may allow once daily dosing of d4T in older children able to swallow pills and who can receive adult dosing	• d4T associated with higher incidence of hyperlactatemia/ lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia • Single mutation confers 3TC resistance
Alternative Combinations		
ABC plus ZDV	• Palatable liquid formulations • Can give with food	• Potential for ABC hypersensitivity reaction • Bone marrow suppression with ZDV
ABC plus 3TC	• Palatable liquid formulations • Can give with food	• Potential for ABC hypersensitivity reaction • Single mutation confers 3TC resistance
ddI plus 3TC	• Videx EC may allow once daily dosing of ddI in older children able to swallow pills and who can receive adult dosing	• Food effect (ddI needs to be taken 1 hour before or 2 hours after food) • Pancreatitis, neurotoxicity with ddI, potentially additive with 3TC • Single mutation confers 3TC resistance

Table 8: two of two Pages

Table 8. Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Combinations for Use in Highly Active Antiretroviral Combination Regimens

NRTI (cont)	Advantages	Disadvantages
Use in Special Circumstances		
d4T plus ddI	• Can give with food • Videx EC may allow once daily dosing of ddI in older children able to swallow pills and who can receive adult dosing • Zerit XR may allow once daily dosing of d4T in older children able to swallow pills and who can receive adult dosing	• d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia than other NRTIs • Potential synergistic toxicity (neurotoxicity, lactic acidosis, hepatic steatosis) of the combination • Food effect (ddI needs to be taken 1 hour before or 2 hours after food)
ZDV plus ddC	• Can give with food	• No liquid formulation ddC • ddC less potent NRTI than other NRTIs • Bone marrow suppression with ZDV • Severe peripheral neuropathy from ddC
Insufficient Data to Make Recommendation		
Tenofovir	• Resistance slow to develop • Once daily dosing for tenofovir (adults) • Less mitochondrial toxicity than NRTIs • Can give with food	• No data on pediatric dosing or safety • Potential bone and renal toxicity • ddI concentrations are increased when given with tenofovir, potential for increased toxicity of ddI
FTC	• Once daily dosing (adults) • Can give with food	• No data on pediatric dosing or safety • No liquid formulation
Not Recommended		
ZDV plus d4T		• Pharmacologic and antiviral antagonism
ddC plus d4T		• Potentially synergistic neurotoxicity • No liquid formulation ddC
ddC plus ddI		• Potentially synergistic neurotoxicity • No liquid formulation ddC
ddC plus 3TC		• Potentially synergistic neurotoxicity • No liquid formulation ddC

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

Table 9. Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens

	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 among NNRTIs • 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), although less than with protease inhibitors
Strongly Recommended		
Efavirenz (for children >3 years old or 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) • 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
Insufficient Data to Recommend		
Delavirdine	• Can give with food	• No liquid formulation • No pediatric studies, so dose not established in children

NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor

Table 10: one of two pages

Table 10. Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens

	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
Strongly Recommended		
Lopinavir/ ritonavir	• Coformulated liquid and capsule formulations • Can give with food	• Poor palatability of liquid (bitter taste), although better than ritonavir alone • Food effect (should be administered with food) • Ritonavir component associated with large number of drug interactions (see ritonavir)
Nelfinavir	• Powder formation (for liquid preparation) • Few adverse effects • Can give with food	• Diarrhea • Powder formulation poorly tolerated • Food effect (should be administered with food) • Appropriate dosage for younger children not well-defined • Need for 3-times daily dosing for younger children
Ritonavir	• Liquid formulation • Can give 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)
Alternative		
Indinavir		• Only available in capsule • Possible higher incidence nephrotoxicity in children • Requires 3-times daily dosing • High fluid intake required • Food effect (should be taken 1 hour before or 2 hours after food) • Lack of pediatric pharmacokinetic data
Amprenavir	• Can give with food	• Poor palatability of liquid (bitter taste) • Due to potential toxicity from high amounts of propylene glycol in oral solution, cannot use in children <4 years • Skin rash • Large volume of liquid formulation required

Table 10: two of two pages

Table 10. Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens

Insufficient Data to Recommend		
Fosamprenavir	• Oral prodrug of amprenavir with lower pill burden • Can give with food	• Skin rash
Saquinavir soft-gel capsule		• Should not be used as sole protease inhibitor in children • Limited information on appropriate dosing in children; will require boosting with another protease inhibitor (e.g., ritonavir) to achieve adequate concentrations, but pharmacokinetic data in children on appropriate dosing of combination not available • Only available in capsule • High pill burden • Must be taken with food • Photosensitivity reactions can occur
Saquinavir hard-gel capsule		• Should not be used as sole protease inhibitor in children • Limited information on appropriate dosing in children; will require boosting with another protease inhibitor (e.g., ritonavir) to achieve adequate concentrations, but pharmacokinetic data in children on appropriate dosing of combination not available • Only available in capsule • High pill burden • Poor bioavailability; must be taken with food
Atazanavir	• Once daily dosing (adults) • Minimal effect on triglyceride and total cholesterol levels than other protease inhibitors (adults)	• No data on pediatric dosing or safety • 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)

Table 11. Recommended Antiretroviral Regimens for Initial Therapy for Human Immunodeficiency Virus (HIV) Infection in Children

Protease Inhibitor-Based Regimens	
Strongly Recommended:	Two NRTIs[1] ***plus*** Lopinavir/ritonavir ***or*** Nelfinavir ***or*** Ritonavir
Alternative Recommendation:	Two NRTIs[1] ***plus*** Amprenavir (children ≥4 years old)[2] ***or*** Indinavir
Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens	
Strongly Recommended:	Children > 3 years: Two NRTIs[1] ***plus*** Efavirenz[3] (with or without Nelfinavir)
	Children ≤3 years or who can't swallow capsules: Two NRTIs[1] ***plus*** Nevirapine[3]
Alternative Recommendation:	Two NRTIs[1] ***plus*** Nevirapine[3] (children >3 years)
Nucleoside Analogue-Based Regimens	
Strongly Recommended:	None
Alternative Recommendation:	Zidovudine ***plus*** Lamivudine ***plus*** Abacavir
Use in Special Circumstances:	Two NRTIs[1]
Regimens that are Not Recommended	
	Monotherapy[4]
	Certain two NRTI combinations[1]
	Two NRTIs ***plus*** Saquinavir soft or hard gel capsule as a sole protease inhibitor[5]
Insufficient Data to Recommend	
	Two NRTIs[1] ***plus*** Delavirdine
	Dual protease inhibitors, including saquinavir soft or hard gel capsule with low dose ritonavir, with the exception of lopinavir/ritonavir[4]
	NRTI ***plus*** NNRTI ***plus*** protease inhibitor[6]
	Tenofovir-containing regimens
	Enfuvirtide (T-20)-containing regimens
	Emtricitabine (FTC)-containing regimens
	Atazanavir-containing regimens
	Fosamprenavir-containing regimens

[1] Dual NRTI combination recommendations:
Strongly Recommended choices: Zidovudine plus didanosine or lamivudine; or stavudine plus lamivudine
Alternative Choices: Abacavir plus zidovudine or lamivudine; or didanosine plus lamivudine
Use in Special Circumstances: Stavudine plus didanosine; or zalcitabine plus zidovudine
Insufficient Data: Tenofovir- or emtricitabine-containing regimens
Not Recommended: Zalcitabine plus didanosine, stavudine, or lamivudine; or zidovudine plus stavudine

[2] Amprenavir should not be administered to children under age 4 years due to the propylene glycol and vitamin E content of the oral liquid preparation and lack of pharmacokinetic data in this age group (see **Appendix** and **Antiretroviral Drug hyperlink**).

[3] Efavirenz is currently available only in capsule form, although a liquid formulation is currently under study to determine appropriate dosage in HIV-infected children under age 3 years; nevirapine would be the preferred NNRTI for children under age 3 years or who require a liquid formulation.

[4] Except for zidovudine chemoprophylaxis administered to HIV-exposed infants during the first 6 weeks of life to prevent perinatal HIV transmission; if an infant is confirmed as HIV-infected while receiving zidovudine prophylaxis, therapy should either be discontinued or changed to a combination antiretroviral drug regimen.

[5] With the exception of lopinavir/ritonavir, data on the pharmacokinetics and safety of dual protease inhibitor combinations (e.g., low dose ritonavir pharmacologic boosting of saquinavir, indinavir, or nelfinavir) are limited, use of dual protease inhibitors as a component of initial therapy is not recommended, although such regimens may have utility as secondary treatment regimens for children who have failed initial therapy. Saquinavir soft and hard gel capsule require low dose ritonavir boosting to achieve adequate levels in children, but pharmacokinetic data on appropriate dosing are not yet available.

[6] With the exception of efavirenz plus nelfinavir plus 1 or 2 NRTIs, which has been studied in HIV-infected children and shown to have virologic and immunologic efficacy in a clinical trial *[134]*.

NRTI: Nucleoside analogue reverse transcriptase inhibitor
NNRTI: Non-nucleoside analogue reverse transcriptase inhibitor

Table 12. Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children

Virologic Considerations*	• Less than a minimally acceptable virologic response after 8–12 weeks of therapy. For children receiving aggressive antiretroviral therapy, such a response is defined as a less than tenfold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels. • HIV RNA not suppressed to undetectable levels after 4–6 months of antiretroviral therapy. † • Repeated detection of HIV RNA in children who initially had undetectable levels in response to antiretroviral therapy. § • A reproducible increase in HIV RNA copy number among children who have had a substantial HIV RNA response but still have low levels of detectable HIV RNA. Such an increase would warrant change in therapy if, after achieving a virologic nadir, a greater than threefold (>0.5 $\log_{10}$) increase in copy number for children aged $\geq$2 years and greater than fivefold (>0.7 $\log_{10}$) increase is observed for children aged <2 years.
Immunologic Considerations	• Change in immunologic classification (**Table 1**).¶ • For children with $CD4^+$ T cell percentages of <15% (i.e., those in immune category 3), a persistent decline of 5 percentiles or more in $CD4^+$ T cell percentage (i.e., from 15% to 10%). • A rapid and substantial decrease in absolute $CD4^+$ T cell count (i.e., >30% decline in <6 months).
Clinical Considerations	• Progressive neurodevelopmental deterioration. • Growth failure defined as persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation. • A disease progression defined as advancement from one pediatric clinical category to another (i.e., from clinical category A to clinical category B).**

* 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 to 2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels.

§ Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., less than 5,000 copies/mL). The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations.

¶ Minimal changes in $CD4^+$ T cell percentile that may result in change in immunologic category (i.e., from 26% to 24%, or 16% to 14%) may not be as concerning as a rapid substantial change in $CD4^+$ T cell percentile within the same immunologic category (i.e., a drop from 35% to 25%).

** In patients with stable immunologic and virologic parameters, progression from one clinical category to another may not represent an indication to change therapy. Thus, in patients whose disease progression is not associated with neurologic deterioration or growth failure, virologic and immunologic considerations are important in deciding whether to change therapy.

Figure 1. Estimated probability of developing AIDS within 12 months at selected ages by CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from 43].*

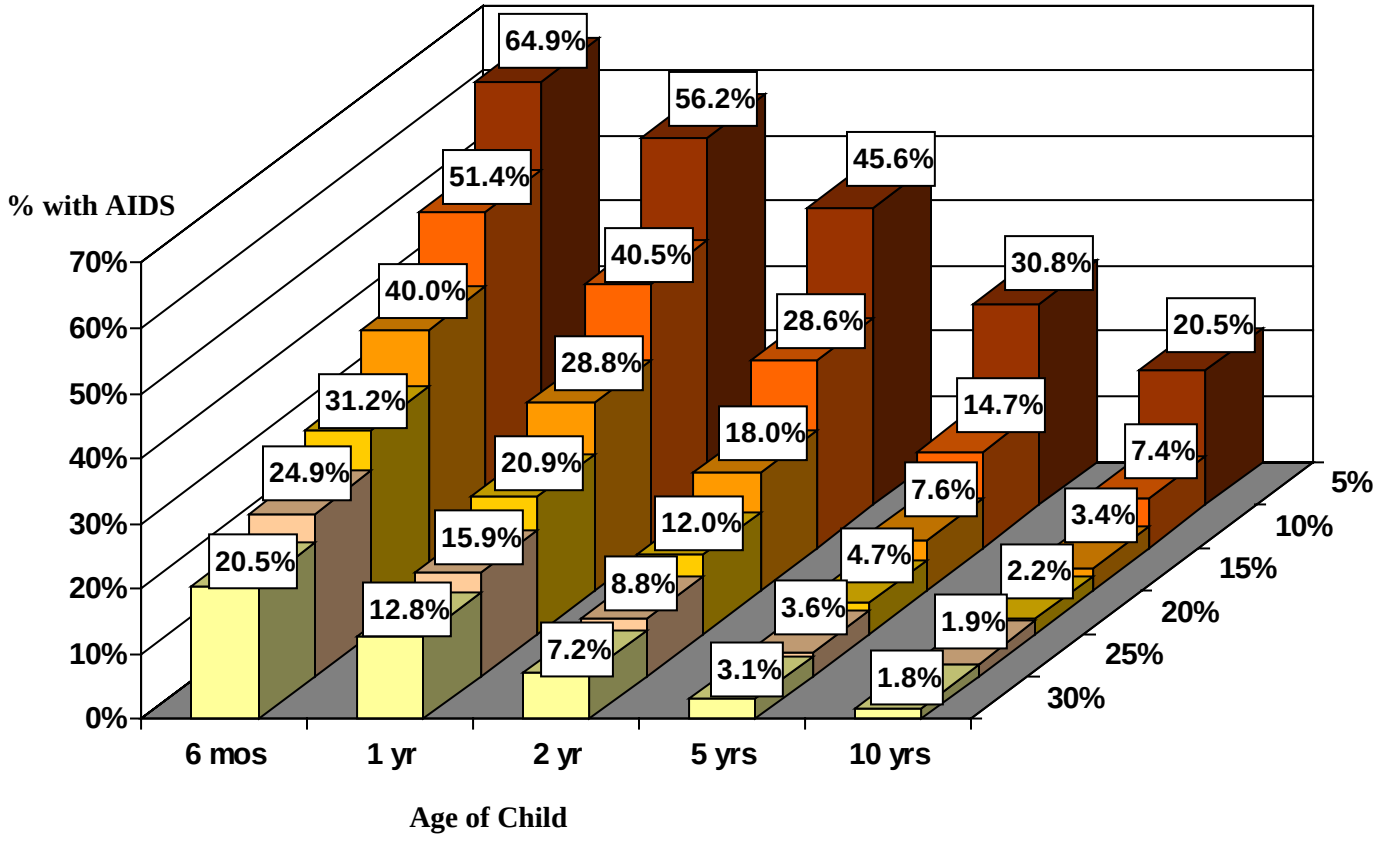


Figure 2. Estimated probability of death within 12 months at selected ages by CD4 percentage in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from 43].*

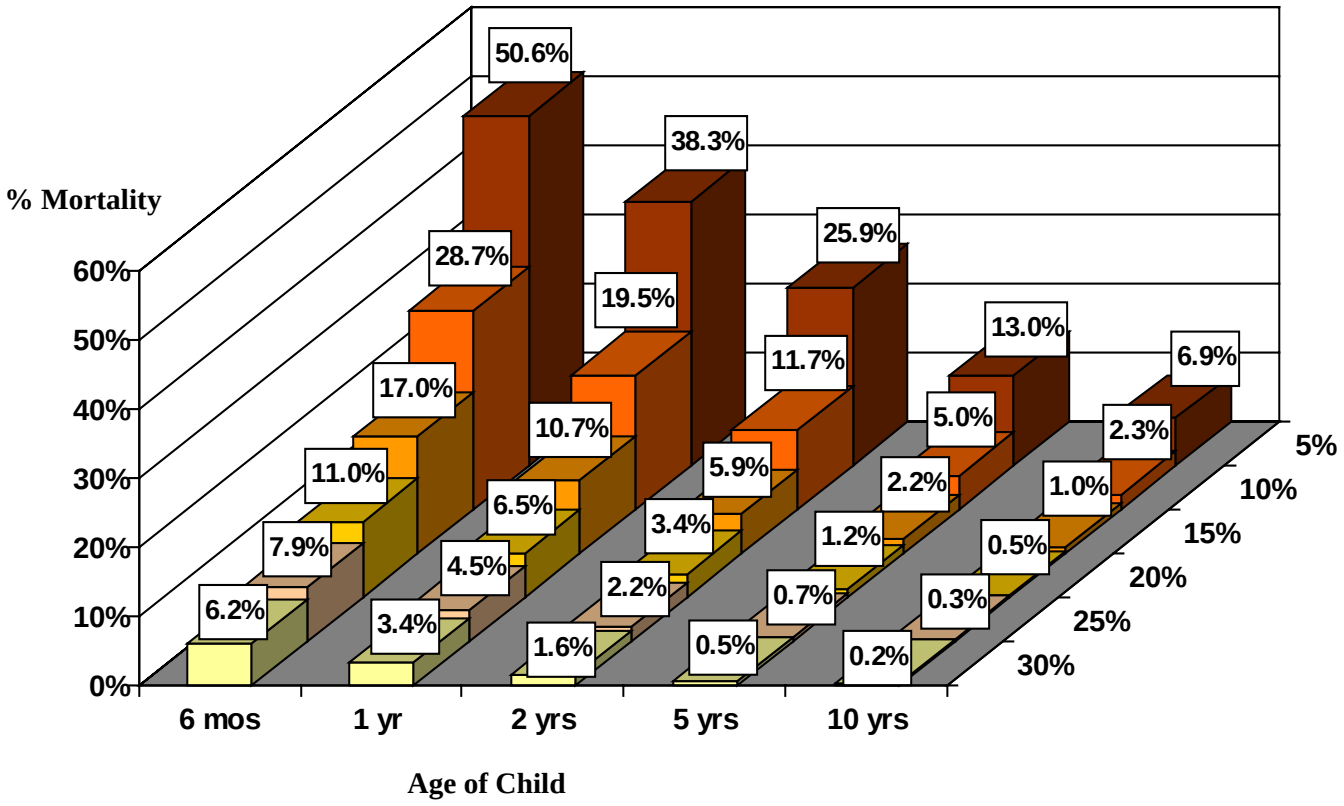


Figure 3. Estimated probability of developing AIDS within 12 months at selected ages by HIV RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from 43].*

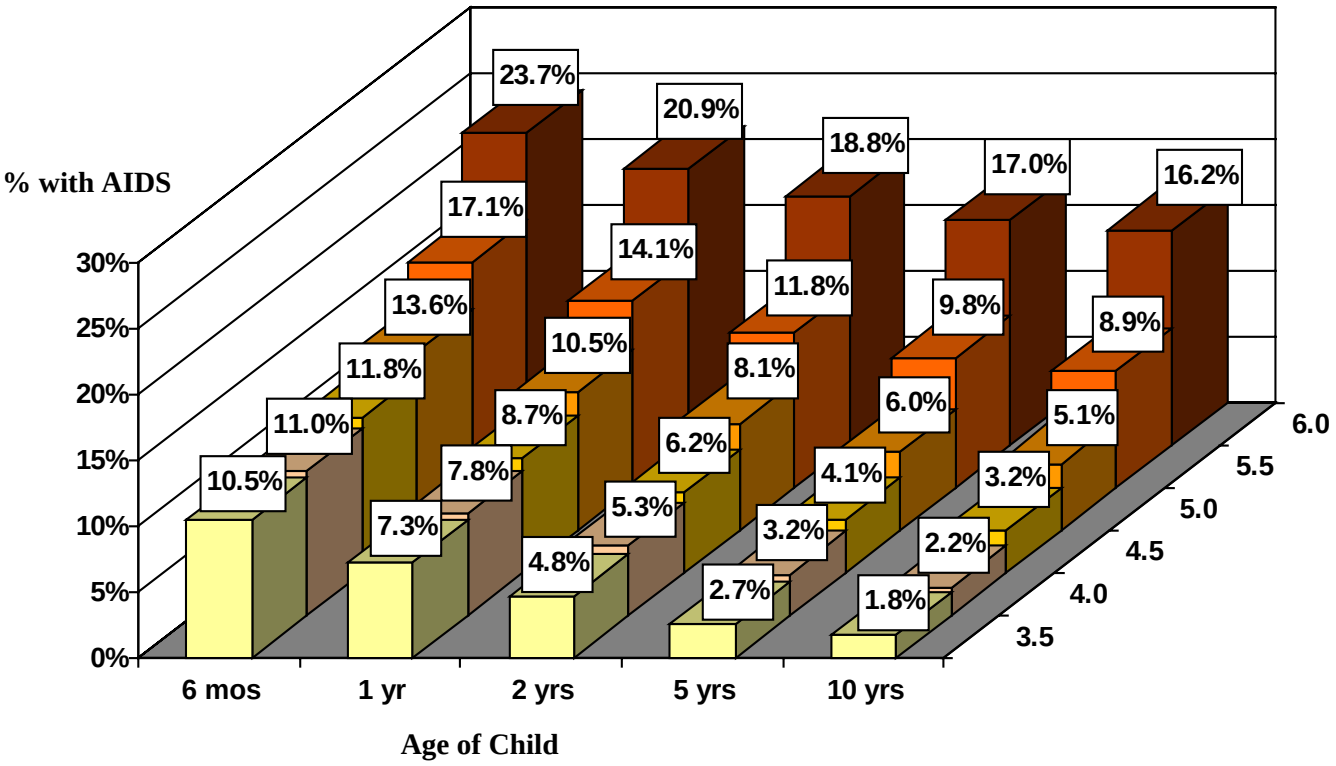
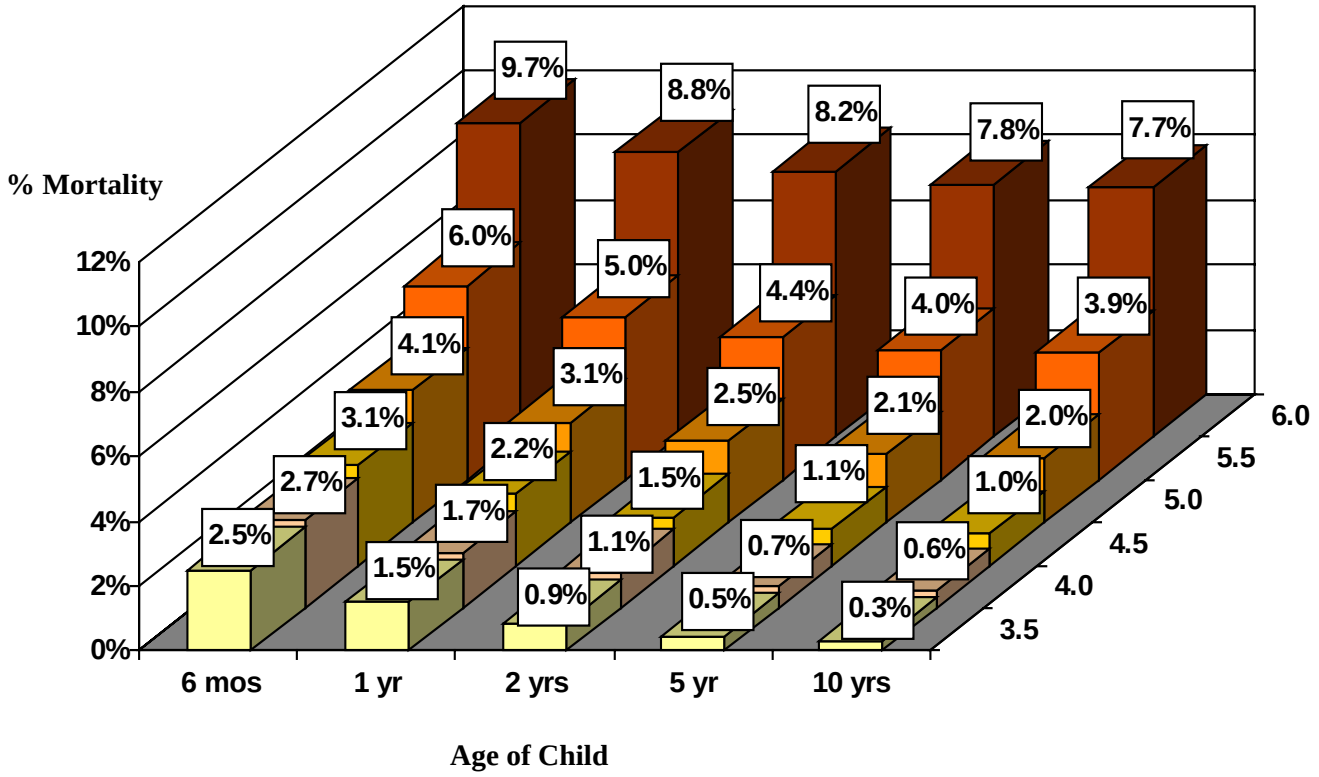


Figure 4. Estimated probability of death within 12 months at selected ages by HIV RNA copy number in HIV-infected children receiving no therapy or zidovudine monotherapy *[modified from 43].*



APPENDIX
Characteristics of Available Antiretroviral Drugs

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

Abacavir *(GW 1592U89, ABC, Ziagen™)*
URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Pediatric oral solution: 20 mg/mL; Tablets: 300 mg

Tablets in combination with zidovudine and lamivudine: TRIZIVIR- 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

Dosage
Neonatal/Infant dose: Not approved for infants less than three months of age. In infants between one and three months of age, a dose of 8 mg/kg of body weight twice daily is under study.

Pediatric/Adolescent dose: 8 mg/kg of body weight twice daily, maximum dose 300 mg twice daily.

Adult dose: 300 mg twice daily.

Adult dose of TRIZIVIR: 1 tablet twice daily.

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

Less common (more severe): Approximately 5% of adults and children receiving ABC develop a potentially fatal hypersensitivity reaction. Symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhea, and abdominal pain or respiratory symptoms such as shortness of breath. Physical findings include lymphadenopathy, ulceration of mucous membranes, and maculopapular or urticarial skin rash. The hypersensitivity reaction can occur without a rash.

Laboratory abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia. This reaction generally occurs in the first six weeks of therapy. Patients suspected of having a hypersensitivity reaction should have ABC stopped and not restarted since hypotension and death have occurred upon rechallenge. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Rare: Pancreatitis, increased liver enzymes, elevated blood glucose, elevated triglycerides, and fatigue.

Drug Interactions
- No significant interactions between ABC, ZDV, and 3TC.
- ABC does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Thus, it should not cause changes in drug levels or clearance of agents metabolized through these pathways, such as PIs and NNRTIs.
- Ethanol decreases elimination of ABC, resulting in a modest increase in drug exposure.

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).
- Patients should not interrupt therapy without consulting with their physician.

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* Information in this appendix is not all inclusive. Complete and detailed prescribing and toxicity information on 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 I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their 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.

Didanosine *(dideoxyinosine, ddI, Videx®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL; Chewable tablets with buffers: 25, 50, 100, 150 mg, and 200mg; Buffered powder for oral solution: 100, 167, and 250 mg; Delayed-release capsules (enteric-coated beadlets): VIDEX EC- 125, 200, 250, and 400 mg.

Dosage

Neonatal/Infant dose (infants aged <90 days): 50 mg per m^2 of body surface area every 12 hours.

Pediatric usual dose: In combination with other antiretrovirals: 120 mg per m^2 of body surface area every 12 hours.

Pediatric dosage range: 90 to 150 mg per m^2 of body surface area every 12 hours (Note: may need higher dose in patients with central nervous system disease.)

Adolescent/Adult dose: Body weight ≥60 kg: 200 mg twice daily. Body weight <60 kg: 125 mg twice daily. May be administered once daily in adolescents/adults to improve compliance, however, twice daily dosing provides better therapeutic response than once daily dosing.

VIDEX EC: Adolescent/Adult dose: Body weight >60 kg: 400 mg once daily. Body weight <60 kg: 250 mg once daily.

Major Toxicities

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

Less common (more severe): Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Rare: Pancreatitis (dose related, less common in children than adults), increased liver enzymes, and retinal depigmentation.

Drug Interactions

- Possible decrease in absorption of ketoconazole, itraconazole, and dapsone; administer at least two hours before or two hours after ddI.
- Tetracycline and iron salts should be given one hour before or four hours after ddI.
- Fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets); administer two hours before or four to eight hours after ddI (varies with fluoroquinolone antibiotic).
- Concomitant administration of ddI and DLV may decrease the absorption of these drugs; separate dosing by at least two hours.
- Administration with PIs: IDV should be administered at least one hour before ddI on an empty stomach. RTV and ATV should be administered at least two hours before or one hour after ddI. NFV should be administered at least one hour after ddI.
- Tenofovir should be administered two hours before or one hour after ddI. The combination may cause increased ddI levels and therefore a higher risk of toxicity.

Special Instructions

- ddI formulation contains buffering agents or antacids.
- Food decreases absorption; administer ddI on an empty stomach (30 minutes before or two hours after a meal). For oral solution: shake well and keep refrigerated; admixture is stable for 30 days.
- When administering chewable tablets, at least two tablets should be administered to ensure adequate buffering capacity (i.e., if the child's dose is 50 mg, administer two 25 mg tablets and not one 50 mg tablet).
- Buffered powder is not suitable for once daily dosing except in patients with renal impairment.
- Decreased dosage should be used for patients with impaired renal function.

Emtricitabine *(FTC, Emtriva™)*

Preparations: Capsules: 200 mg.

Dosage

Neonatal/Infant dose: Unknown.

Pediatric dose: Not approved in children <18 years; phase I/II studies underway in children.

Adolescent (≥18 years)/Adult dose: 200 mg once daily.

Major Toxicities

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

Less common (more severe): Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions
- No inhibition of CYP450 isoenzymes or hepatic glucuronidation enzyme.
- Competition with other compounds that undergo renal elimination (possible competition for renal tubular secretion).

Special Instructions
- Can be administered with food.
- Decrease dosage in patients with impaired renal function.
- Patients should be screened for chronic hepatitis B virus (HBV) infection before starting therapy; exacerbation of hepatitis B 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.

Lamivudine *(3TC, Epivir®, Epivir HBV®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Solution: 5 mg/mL (Epivir HBV), 10 mg/mL; Tablets: 100 (Epivir HBV), 150, 300 mg.

Tablets in combination with zidovudine: COMBIVIR– 300 mg zidovudine and 150 mg lamivudine.

Tablets in combination with zidovudine and abacavir: TRIZIVIR- 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

Dosage

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 twice daily.

Adolescent/Adult dose: Body weight ≥50 kg: 150 mg twice daily or 300 mg once daily. Body weight <50 kg: 2 mg per kg of body weight twice daily.

Adolescent/Adult dose of COMBIVIR: one tablet twice daily.

Adolescent/Adult dose of TRIZIVIR: one tablet twice daily.

Major Toxicities

More common: Headache, fatigue, nausea, diarrhea, skin rash, and abdominal pain.

Less common (more severe): Pancreatitis (primarily seen in children with advanced HIV infection receiving multiple other medications), peripheral neuropathy, decreased neutrophil count, and increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions
- Trimethoprim/sulfamethoxazole (TMP/SMX) increases 3TC blood levels (possibly competes for renal tubular secretion); unknown significance.
- When used with ZDV may prevent emergence of ZDV resistance, and for ZDV-resistant virus, revision to phenotypic ZDV sensitivity may be observed.

Special Instructions
- Can be administered with food.
- For oral solution: store at room temperature.
- Decrease dosage in patients with impaired renal function.

Stavudine *(d4T, Zerit®, Zerit XR®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Solution:1 mg/mL; Capsules: 15, 20, 30, and 40 mg; Extended-release capsules (Zerit XR): 75 and 100 mg.

Dosage

Neonatal/Infant dose: Under evaluation in Pediatric AIDS Clinical Trial Group protocol 332.

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

Adolescent/Adult dose: Body weight ≥60 kg: 40 mg twice daily. Body weight <60 kg: 30 mg twice daily.

Zerit XR capsules (adult dose): Body weight ≥60 kg: 100 mg once daily. Body weight <60 kg: 75 mg once daily.

Major Toxicities

More common: Headache, gastrointestinal disturbances, and skin rashes.

Less common (more severe): Peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Rare: Increased liver enzymes.

Drug Interactions
- Drugs that decrease renal function could decrease clearance.
- Should not be administered in combination with ZDV (poor antiretroviral effect).

Special Instructions
- Can be administered with food.
- Need to decrease dose in patients with renal impairment.
- For oral solution: shake well and keep refrigerated; solution stable for 30 days.

Tenofovir *(Viread®)*
URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 300 mg

Dosage
Neonatal/Infant dose: Unknown

Pediatric dose: Safety and effectiveness in pediatric patients have not been established. Current indication is for patients 18 years of age and older. Phase I study in pediatric patients is underway.

Adult dose: 300 mg once daily.

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 with the use of nucleoside analogs.

Rare (unknown): Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. These effects have not been seen in adult patients taking tenofovir for up to one year. It is not known if these effects will be seen in persons taking tenofovir for more than one year or in children. Evidence of renal toxicity including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calcuria and decreases in serum phosphate has been observed in animal studies at high exposure levels. Tenofovir-associated renal toxicity has not been observed in clinical studies of patients on treatment for up to one year. The long-term renal effects are not known but patients at risk should be closely monitored.

Drug Interactions
- Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir.
- ddI serum concentrations are increased when coadministered with tenofovir and patients should be monitored for ddI toxicity.
- Tenofovir may decrease ATV plasma concentrations; further investigation into this drug interaction is needed. In adults, ATV plus a boosting dose of 100 mg ritonavir may be required if coadministered with tenofovir.
- Tenofovir should be given two hours before or one hour after ddI formulations.

Special Instructions
- Administer with food. High fat meal increases absorption.
- Decreased dosage should be used in patients with impaired renal function.
- Tenofovir should not be administered to patients with renal insufficiency (creatinine clearance <60 mL/min) until prescribing data is available in this patient population.
- Safety and effectiveness in pediatric patients has not been established.

Zalcitabine *(ddC, HIVID®)*
URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 0.375 and 0.75 mg.

Dosage
Neonatal/Infant dose: Unknown

Pediatric usual dose: 0.01 mg per kg of body weight every eight hours.

Adolescent/Adult dose: 0.75 mg three times a day.

Major Toxicities
More common: Headache, gastrointestinal disturbances, and malaise.

Less common (more severe): Peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, and skin rashes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions
- Antacids decrease absorption of ddC.
- Cimetidine, amphotericin, aminoglycosides and foscarnet may decrease renal clearance of ddC.
- Concomitant use with ddI is not recommended because of the increased risk of peripheral neuropathy.

- Intravenous pentamidine increases the risk for pancreatitis; do not use concurrently.

Special Instructions

- Because the presence of food may decrease the rate and extent of absorption, it is recommended that ddC be administered on an empty stomach (one hour before or two hours after a meal).
- Decrease dosage in patients with impaired renal function.

Zidovudine *(ZDV, AZT, Retrovir®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Syrup: 10 mg/mL; *Capsules:* 100 mg; *Tablets:* 300 mg; Concentrate for injection/for intravenous infusion: 10 mg/mL.

Tablets in combination with lamivudine: COMBIVIR- 300 mg zidovudine and 150 mg lamivudine.

Tablets in combination with lamivudine and abacavir: TRIZIVIR- 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

Dosage

Dose for premature infants: (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 eight hours at two weeks of age (neonates $\geq$30 weeks gestational age) or at four weeks (neonates <30 weeks gestational age).

Neonatal/Infant dose (infants aged <90 days): Oral: 2 mg per kg of body weight every six hours.

Intravenous: 1.5 mg per kg of body weight every six hours.

Pediatric usual dose: Oral: 160 mg per m^2 of body surface area every eight hours.

Intravenous (intermittent infusion): 120 mg per m^2 of body surface area every six hours.

Intravenous (continuous infusion): 20 mg per m^2 of body surface area per hour.

Pediatric dosage range: 90 mg per m^2 of body surface area to 180 mg per m^2 of body surface area every six to eight hours.

Adolescent/Adult dose: 200 mg three times a day or 300 mg twice daily.

Adolescent/Adult dose of TRIZIVIR: one tablet twice daily.

Major Toxicities

More common: Hematologic toxicity, including granulocytopenia and anemia, and headache.

Less common: Myopathy, myositis, and liver toxicity.

Unusual (severe): Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions

- Increased toxicity may be observed with concomitant administration of the following drugs (therefore, more intensive toxicity monitoring may be warranted): ganciclovir, interferon-alpha, TMP/SMX, acyclovir, and other drugs that can be associated with bone marrow suppression.
- The following drugs may increase ZDV concentrations (and therefore potential toxicity): probenecid, atovaquone, methadone, valproic acid, and fluconazole.
- Decreased renal clearance may be observed with co-administration of cimetidine (may be significant in patients with renal impairment).
- ZDV metabolism may be increased with coadministration of rifampin and rifabutin (clinical significance unknown); clarithromycin may decrease concentrations of ZDV probably by interfering with absorption (preferably administer four hours apart).
- Ribavirin decreases the intracellular phosphorylation of ZDV (conversion to active metabolite).
- Phenytoin concentrations may increase or decrease.
- Should not be administered in combination with d4T (poor antiretroviral effect).

Special Instructions

- Can be administered with food (although the manufacturer recommends administration 30 minutes before or one hour after a meal).
- Decrease dosage in patients with severe renal impairment.
- 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.
- Reduced dosage may be indicated in patients with substantial hepatic dysfunction.
- Infuse intravenous loading dose or intermittent infusion dose over one hour.
- For intravenous solution: dilute with 5% dextrose injection solution to concentration $\leq$4 mg/mL; refrigerated diluted solution is stable for 24 hours.

- Some experts in pediatric HIV infection use a dose of 180 mg per m^2 of body surface area every 12 hours when using in drug combinations with other antiretroviral compounds, but data on this dosing in children is limited.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIS)* †

Delavirdine *(DLV, Rescriptor®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 100 mg and 200 mg.

Dosage

Neonatal/Infant dose: Unknown.

Pediatric dose: Unknown.

Adolescent/Adult dose: 400 mg three times a day or 600 mg twice daily (investigational).

Major Toxicities

More common: Headache, fatigue, gastrointestinal complaints, and rash (may be severe).

Drug Interactions

- Metabolized in part by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.§
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- DLV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. DLV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine), sedative-hypnotics (i.e., alprazolam, midazolam, or triazolam), calcium channel blockers (i.e., nifedipine), ergot alkaloid derivatives, amphetamines, cisapride, or warfarin.
- DLV clearance is increased, resulting in substantially reduced concentrations of DLV, with concurrent use of rifabutin, rifampin, or anticonvulsants (i.e., phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.
- Absorption of DLV is decreased if given with antacids or $histamine_2$ receptor antagonists.
- Increased trough concentrations of DLV if given with ketoconazole or fluoxetine; increased levels of both drugs if DLV is given with clarithromycin.
- DLV increases levels of dapsone and quinidine.
- Administration with protease inhibitors: decreases metabolism of SQV and IDV, resulting in a significant increase in SQV and IDV concentrations and a slight decrease in DLV concentrations.

Special Instructions

- Can be administered with food.
- Should be taken one hour before or one hour after ddI or antacids.
- The 100 mg tablets can be dissolved in water and the resulting dispersion taken promptly. However, the 200 mg tablets should be taken as intact tablets, because they are not readily dispersed in water.

Efavirenz *(DMP-266, EFV, Sustiva™)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Capsules: 50, 100, and 200 mg. Tablets: 600 mg.

Dosage

Neonatal/Infant dose: Unknown

Pediatric dose: Administered once daily. Body weight 10 to <15 kg: 200 mg; 15 to <20 kg:250 mg; 20 to <25 kg: 300 mg; 25 to <32.5 kg: 350 mg; 32.5 to <40 kg: 400 mg; ≥40 kg:600 mg. There are

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* Information in this appendix is not all-inclusive. Complete and detailed prescribing and toxicity information on 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 I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their 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, some of which may be life-threatening with multiple drugs. 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 those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

currently no data available on the appropriate dosage for children under age three years.

Adult/Adolescent dose: 600 mg once daily

Major Toxicities

More common: Skin rash; central nervous system (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria), primarily reported in adults; increased aminotransferase levels, teratogenic in primates (use in pregnancy should be avoided and women of childbearing potential should undergo pregnancy testing before initiating therapy).

Drug Interactions

- Mixed inducer/inhibitor of cytochrome P450 3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on specific enzyme pathway involved.
- Not recommended for concurrent use: antihistamines (i.e., astemizole or terfenadine), sedative-hypnotics (i.e., midazolam or triazolam), cisapride, or ergot alkaloid derivatives.
- Drug interactions requiring careful monitoring if coadministered: warfarin (levels potentially increased or decreased); ethinyl estradiol (levels potentially increased; while of uncertain clinical significance, a reliable method of barrier contraception should be used in addition to oral contraceptives).
- Enzyme inducers such as rifampin, rifabutin, phenobarbital and phenytoin may decrease EFV concentrations; clinical significance is unknown.
- EFV is highly plasma protein bound, and has the potential for drug interactions with other highly protein bound drugs (i.e., phenobarbital and phenytoin).
- Clarithromycin levels are decreased while the levels of its metabolite are increased; alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics have not been studied in combination with EFV.
- Numerous drug interactions when EFV is administered in combination with protease inhibitors: Coadministration decreases levels of ATV (area under the curve [AUC] decreased by 74%), SQV (AUC decreased by 50%) and IDV (AUC decreased by 31%). If EFV is coadministered with ATV, low dose RTV boosting is recommended (300 mg ATV/100 mg RTV) in adults (all drugs given together as a single daily dose with food). Coadministration of SQV as a sole PI is not recommended; IDV dose should be increased if given with EFV (for adults, 1000 mg every eight hours). Coadministration increases levels of both RTV and EFV (AUC increased by 20% for both), and is associated with a higher frequency of adverse clinical and laboratory findings; monitoring of liver enzymes is recommended if coadministered. Coadministration increases levels of NFV (AUC increased by 20%) but no dose adjustment is needed. EFV lowers LPV/r plasma concentrations and higher doses of LPV/r are recommended when used in combination.

Special Instructions

- Efavirenz can be taken with and without food. The relative bioavailability of EFV was increased by 50% (range 11-126%) following a high fat meal (1070 kcal, 82 grams fat, 62% of calories from fat - this is equivalent to an intake of 8.2 Milky Way candy bars in one sitting). Because there is no information on 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.
- Capsules may be opened and added to liquids or foods, but EFV has a peppery taste; grape jelly has been used to disguise the taste.
- Bedtime dosing is recommended, particularly during the first two to four weeks of therapy, to improve tolerability of central nervous system side effects.

Nevirapine *(NVP, Viramune®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

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

Dosage

NVP is initiated at a lower dose and increased in a step-wise fashion. This allows induction of cytochrome P450 3A, which results in increased clearance of drug. The occurrence of rash may be diminished by the stepwise increase in dosage. The following suggested incremental increases in dose are given for days on treatment (not age).

Neonatal/Infant dose (through age two months): Under study in Pediatrics AIDS Clinical Trial Group protocol 356: 5 mg/kg of body weight or 120 mg/m^2 of body surface area once daily for 14 days,

followed by 120 mg/m^2 of body surface area every 12 hours for 14 days, followed by 200 mg/m^2 of body surface area every 12 hours.

Pediatric dose: * 120-200 mg/m^2 every 12 hours.

Note: Initiate therapy with 120 mg/m^2 (maximum 200 mg) administered once daily for 14 days. Increase to full dose (120-200 mg/m^2) administered every 12 hours (maximum 200 mg every 12 hours) if no rash or other untoward effects.

OR

7 mg/kg every 12 hours < eight years of age

4 mg/kg every 12 hours > eight years of age

Note: Initiate therapy with daily dose for 14 days and increase to full dose if no rash or other untoward effects.

Adolescent/Adult dose: 200 mg every 12 hours.

Note: Initiate therapy with 200 mg given once daily for the first 14 days. Increase to full dose administered every 12 hours if there is no rash or other untoward effects.

Major Toxicities (continuous dosing, not single dose regimens)

More common: (similar to adults) Skin rash (some severe, requiring hospitalization, and life-threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis), fever, nausea, headache, and abnormal liver function tests.

Less common: Inflammation of the liver (hepatitis), which rarely may lead to severe and life threatening and in some cases fatal liver damage, and very rarely fatal liver failure and granulocytopenia. Hypersensitivity reactions (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/or significant hepatic abnormalities).

Drug Interactions

- Induces hepatic cytochrome P450 3A (CYP3A); autoinduction of metabolism occurs in two to four weeks with a 1.5-fold to twofold increase in clearance. There could potentially be multiple drug interactions. **
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- *Administration with PIs:* IDV and SQV (hard and soft gel formulations) concentrations are decreased significantly (approximately 25%-30%) when administered with NVP. SQV-HGC (Invirase) is not recommended for use in children and is recommended only in combination with RTV in adults. The adult guidelines recommend that IDV doses be increased by 20% when administered in combination with NVP, while recommending standard doses of NFV or RTV in combination with NVP. Data on specific dosing adjustments in pediatric patients for ATV, IDV and NFV are lacking. NVP lowers LPV/r concentrations and higher doses of LPV/r are recommended when used in combination.
- Antifungals: NVP significantly reduces ketoconazole concentrations and these drugs should not be use concomitantly. If indicated, an alternate antifungal agent, such as fluconazole, should be used.
- Rifampin/Rifabutin: Rifampin significantly decreases NVP concentrations. It is not recommended that these drugs be used together. Rifabutin has less of an effect on NVP concentrations.
- Methadone: Patients on methadone maintenance may experience narcotic withdrawal symptoms when NVP is added to their regimen. If withdrawal symptoms occur, methadone doses should be increased and titrated to patient response.

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* The majority of clinical trials involving infants and children utilized the 120-200 mg/m^2 dosing regimen. The new FDA approved regimen, which uses mg/kg dosing, is based on pharmacokinetic modeling designed to achieve similar plasma concentrations as dosing of 150 mg/m^2. NVP clearance is highest during the first two years of life, decreasing gradually after eight to 12 years of age and approaching adult clearance rates. The new dosing regimen accounts for the changes in clearance that occurs after eight years of age. However, the changes in clearance are gradual and the new mg/kg dosing regimen results in an abrupt 43% decrease in dose size when the 8th birthday is reached. Some clinicians may prefer the mg/m^2 dosing that was utilized in clinical trials.

** Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, with multiple drugs. Some of which 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 those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

- Anticonvulsants and psychotropics: There are no data on the extent of drug interactions with the anticonvulsants phenobarbital, phenytoin, and carbamazepine. Serum concentrations of these agents should be monitored. Many of the psychotropics are metabolized by similar metabolic pathways as NVP and may interact; patients should be monitored carefully when these medications are used concomitantly.
- Oral contraceptives: NVP may reduce plasma concentrations of oral contraceptives and other hormonal contraceptives. Oral contraceptives should not be the only means of birth control when used in patients on NVP.

Special Instructions

- Can be administered with food.
- May be administered concurrently with ddI.
- NVP-associated skin rash usually occurs within the first six weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. NVP should be discontinued immediately in patients who develop severe rash or a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering).
- Severe, life-threatening, and in some cases fatal, hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in NVP-treated patients. Increased serum transaminase levels or a history of hepatitis B or C infection prior to starting NVP are associated with higher risk for hepatic adverse events. The majority of cases have occurred during the first 12 weeks of NVP therapy, and 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 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.
- For suspension: Must be shaken well; store at room temperature.

Protease Inhibitors (PIs) * † §

Amprenavir (*APV, Agenerase™*)

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Pediatric oral solution: 15mg/mL; *Capsules:* 50 and 150mg.

Dosage

Neonatal/Infant dose: Not recommended in children <4 years of age.

Pediatric/Adolescent dose (<50kg): For children 4-12 years of age or 13-16 years olds weighing less than 50 kg: *Oral Solution:* 22.5 mg/kg twice daily hours or 17mg/kg three times daily (maximum daily dose 2,800 mg). *Capsules:* 20 mg/kg twice daily or 15 mg/kg three times daily (maximum daily dose 2,400 mg).

Adult dose: 1,200 mg (eight 150 mg capsules) bid

Combination with ritonavir (adults): APV 600 mg + RTV 100 mg twice daily, or APV 1200 mg + RTV 200 mg once daily

Major Toxicities

More common: Vomiting, nausea, diarrhea, perioral parethesias, and rash.

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

Rare: New onset diabetes mellitus, hyperglycemia, exacerbation of preexisting diabetes mellitus, hemolytic anemia, and spontaneous bleeding in hemophiliacs.

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* Information in this appendix is not all inclusive. Complete and detailed prescribing and toxicity information on 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 I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their 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.

§ Data in children is limited, and doses may change as more information is obtained about the pharmacokinetics of these drugs in children.

Drug Interactions

- APV is a substrate for and inhibitor of the cytochrome P450 isoenzyme CYP3A4. There could potentially be multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Coadministering EFV and APV lowers levels of APV 39% *[198]*.
- APV should not be administered concurrently with astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, midazolam, rifampin and triazolam.
- Although no interaction studies have been conducted, serious drug interactions could occur between amiodarone, lidocaine, tricyclic antidepressants, quinidine and warfarin. It is recommended that the concentration of these drugs be monitored when administered concomitantly with APV.
- Rifampin has been found to reduce plasma concentrations of APV (decreased AUC 82%) and should not be used with APV. APV has no significant effect on rifampin plasma levels.
- The AUC of rifabutin is increased by 193% when given in combination with APV. The dose of rifabutin should be reduced by at least half the recommended dose when given in combination with APV.
- Coadministration of APV with sildenafil (Viagra) is likely to result in increased sildenafil concentrations and patients should be advised that they may be at an increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and priapism.
- The FDA approved formulation of APV contains 46 IU vitamin E/mL of oral solution and 109 IU vitamin E-150 mg capsule. The recommended dose of APV results in a dose of 138 IU/kg/day of vitamin E using the oral solution with a maximum dose of 8,587 IU vitamin E per day. Patients receiving the recommended adult dose of APV in capsule form receive 1,744 IU/day of vitamin E. In comparison, the daily recommended dose for vitamin E in children is 10 IU per day and in adults 30 IU per day. Excess ingestion or administration of vitamin E has been associated with creatinuria, decreased platelet aggregation, impaired wound healing, hepatomegaly, prolongation of the Prothrombin Time and the potentiation of vitamin K deficiency coagulopathy. High dose vitamin E may increase the hypoprothrombinemic response to drugs such as warfarin and dicumarol and concurrent use of vitamin E doses >400 IU/day should be avoided in patients taking oral anticoagulants. Patients taking APV should be advised not to take supplemental vitamin E *[199-203]*.
- The liquid formulation of APV contains propylene glycol in a concentration that exceeds WHO standards for use in infants. The serum half-life of propylene glycol in neonates is prolonged at 16.9 hours compared to five hours in adults, due to the immaturity of alcohol dehydrogenase enzyme activity in young infants. High levels of propylene glycol have been associated with hyperosmolarity, lactic acidosis, seizures, and respiratory depression *[204]*.
- The efficacy of hormonal contraceptives may be reduced in patients receiving APV. Alternate or additional methods of birth control should be coadministered if coadministering with hormonal methods of birth control.
- Other medications that are substrates, inhibitors, or inducers of CYP3A4 could also potentially interact with APV. See the product information for Agenerase for complete list of other drugs, which may potentially interact with APV.
- APV is a sulfonamide. The potential for cross sensitivity between drugs in the sulfonamide class and APV is unknown. APV should be used with caution in patients with sulfonamide allergy.

Special Instructions

- APV should not be used in children less than four years of age because of the lack of data in children < 4 years of age, the paucity of data in children in general, the uncertain impact of extremely high doses of vitamin E, and the propylene glycol content of the oral liquid preparation.
- The oral solution and capsule formulation are not interchangeable on a mg per mg basis. The oral bioavailability of the oral solution is 14% less than that of the capsule.
- APV may be taken with or without food, but should not be given with a high fat meal (i.e., 6.7 Milky Way bars) as there is a 21% decrease in the AUC when APV is administered after a high fat meal of 67 grams of fat compared with the fasting state.
- Patients taking antacids (or ddI) should take APV at least one hour before or after antacid (or ddI) use.

Atazanavir *(ATV, Reyataz ™)*

Preparations: Capsule: 100, 150, and 200 mg.

Dosage

Neonatal/infant dose: Should not be administered to infants below the age of 3 months due to the risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose: Not approved in children; phase I/II studies underway in children. Children may require higher doses than adults; dose-finding studies are ongoing to determine the optimal dosing in children.

Adolescent (≥ 16 years)/Adult dose: 400 mg (two 200 mg capsules) once daily. Boosting ATV with ritonavir (RTV) is appropriate when using ATV in combination with tenofovir (TDF) or efavirenz (EFV). Boosting the ATV dose entails combining a 300 mg dose of ATV with 100 mg of RTV, each given once daily. Boosting might be considered for adolescents because adequacy of the adult dose in this age group is not established.

Major Toxicities

More common: Asymptomatic elevations in indirect bilirubin (30% of patients), jaundice (10% of patients), headache, fever, arthralgia, depression, insomnia, dizziness, nausea/vomiting/diarrhea, and paresthesias.

Less common (more severe): Prolongation of PR interval of electrocardiogram.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

Drug Interactions

- 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 CYP1As and CYP2C9. There could potentially be multiple drug interactions.[¶] ATV inhibits the glucuronidation enzyme uridine diphosphate glucuronosyltransferase (UGT1A1).
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- *NRTIs:* TDF decreases ATV plasma concentrations. In adults, it is recommended that ATV 300 mg 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 increases TDF concentrations and could potentiate TDF-associated renal toxicity.
- *NNRTIs:* Coadministration of ATV with EFV decreases ATV levels; EFV levels are unchanged. Therefore, administration of ATV with low dose RTV boost (300 mg ATV plus 100 mg RTV) is recommended in adults receiving EFV. ATV without RTV should not be coadministered with EFV.
- *Protease Inhibitors:* ATV should not be coadministered with IDV due to potential for additive hyperbilirubinemia. Coadministration with low dose RTV ("booster" dose) increases ATV concentration; if coadministered to adults, recommended dose is ATV 300 mg plus RTV 100 mg given once daily with food. Coadministration with saquinavir (SQV) increases SQV concentration; appropriate dosing recommendations for this combination have not been established. In treatment-experienced adults, the combination of ATV plus SQV is not as efficacious as the combination of ATV plus RTV. No data for other PIs.
- *Contraindicated Medications:* Drugs that should not be coadministered with ATV include antihistamines (astemizole, terfenadine); antineoplastics (irinotecan); calcium channel blocker bepridil hydrochloride; ergot alkaloid derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine); HMGCoA reductase inhibitors (such as lovastatin, simvastatin); gastrointestinal drugs (cisapride, proton pump inhibitors such as omeprazole); neuroleptics (pimozide); sedative-hypnotics (midazolam, triazolam); rifampin and rifapentine; and St. John's wort.
- *Sildenafil:* Coadministration of ATV with sildenafil (Viagra) is likely to result in increased sildenafil concentrations; patients should be advised that they could be at increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and priapism.
- *Rifampin:* Rifampin is a potent inducer of CYP3A and may decrease ATV plasma concentrations and

[¶] Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant drug interactions, some life-threatening. These interactions are outlined in detail in prescribing information available from the drug manufacturers, and will not be reiterated in this document. Health care provider, should review manufacturers' documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

reduce its therapeutic effect. Rifampin should not be administered with ATV.

- *Rifabutin:* ATV significantly increases rifabutin concentrations. If administered concomitantly, rifabutin dose reduction of up to 75% is recommended (150 mg every other day or 3 times per week).
- *Cardiac Medications:* Diltiazem plasma concentrations increased twofold when administered with ATV. When administered concurrently, a 50% dose reduction of diltiazem should be considered, and ECG monitoring is recommended. ATV has the potential to prolong the PR interval in some patients, as does diltiazem. An additive effect on the PR interval was observed with concurrent administration of ATV and diltiazem. Caution should be used when administering ATV with medications known to increase the PR interval (atenolol, diltiazem).
- *Antacids:* Antacids and buffered medications (including buffered didanosine formulations) decrease ATV concentrations if administered at the same time. ATV should be administered 2 hours before or 1 hour after these medications.
- *H-2 Receptor Antagonists:* H-2 receptor antagonists are expected to decrease ATV concentrations by interfering with absorption. If given concurrently, separate dosing as far apart as possible, preferably by 12 hours.
- *Proton-Pump Inhibitors:* Coadministration of ATV with proton-pump inhibitors is expected to substantially decrease ATV plasma concentrations and decrease its therapeutic effect. Coadministration of ATV and proton-pump inhibitors is not recommended.
- *Oral contraceptives:* ATV increases concentrations of estradiol and norethindrone; lowest effective dose or alternative methods of contraception should be used.
- *Clarithromycin:* ATV increases clarithromycin levels significantly, which can cause QTc prolongation. Clarithromycin dose should be decreased by 50% or an alternative antimicrobial given.
- *Use With Caution:* Although no interaction studies have been conducted, serious drug interactions could occur between ATV and amiodarone, lidocaine, tricyclic antidepressants, quinidine, and warfarin. It is recommended that concentrations or effects of these drugs be monitored when administered concomitantly with ATV.

Special Instructions

- ATV should be administered with food to enhance absorption.
- ATV does not appear to increase cholesterol or triglyceride levels.
- 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).
- Patients taking antacids (or buffered didanosine formulations) should take ATV at least 2 hours before or 1 hour after antacid (or didanosine) administration.
- ATV is principally metabolized by the liver. Individuals with hepatitis B or C infections and individuals with marked elevations in transaminases prior to treatment may be at increased risk for further elevations in transaminases or hepatic decompensation. Decreased doses should be used in patients with moderate hepatic insufficiency. ATV should not be used in patients with severe hepatic insufficiency.
- Asymptomatic elevations in indirect bilirubin are common in patients receiving ATV. This may be associated with jaundice.

Fosamprenavir *(f-APV, Lexiva®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Tablets: 700 mg fosamprenavir calcium (prodrug, equivalent to 600 mg amprenavir); Suspension (investigational): 50 mg/mL.

Dosage

Pediatric dose: Currently under investigation; insufficient data to recommend a dose.

Adult/Adolescent dose:

Antiretroviral-Naïve Patient

- 1400 mg twice daily (without RTV)
- 1400 mg once daily plus RTV 200 mg once daily
- 700 mg twice daily plus RTV 100 mg twice daily

Protease Inhibitor-Experienced Patient

(note: once daily administration of f-APV plus RTV is not recommended in protease inhibitor-experienced patients)

- 700 mg twice daily plus RTV 100 mg twice daily

Major Toxicities
More common: Vomiting, nausea, diarrhea, perioral parethesias, headache, and rash.

Less common (more severe): Life-threatening rash, including Stevens-Johnson syndrome in <1% of patients; fat redistribution and lipid abnormalities.

Rare: New onset diabetes mellitus, hyperglycemia, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, and spontaneous bleeding in hemophiliacs.

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

- 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 could potentially be multiple drug interactions. Other medications that are substrates, inhibitors, or inducers of CYP3A4 could also potentially interact with APV. See the product information for f-APV for a complete list of other drugs which may potentially interact with APV.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- APV should not be administered concurrently with: certain cardiac drugs (flecainide, propafenone, bepridil); cisapride; neuroleptics (pimozide); ergot alkaloid derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine); antihistamines (astemizole); sedative-hypnotics (midazolam, triazolam); anti-lipid drugs (lovastatin, simvastatin); and rifampin.
- Concomitant use of f-APV with St. John's wort is not recommended. St. John's wort decreases serum concentrations of protease inhibitors, including APV, and could result in suboptimal levels and possible resistance.
- Rifampin has been found to reduce plasma concentrations of APV by 90% and decrease AUC by 82% and should not be used with APV. APV has no significant effect on rifampin plasma levels.
- The AUC of rifabutin is increased by 193% when given in combination with APV. The dose of rifabutin should be reduced by at least half the recommended dose when given in combination with APV. When rifabutin is administered with f-APV plus RTV, dosage reduction of at least 75% is recommended (maximum rifabutin dose of 150 mg every other day or three times per week).
- Concomitant use of lovastatin and simvastatin is not recommended. The risk of myopathy, including rhabdomyolysis, may be increased with protease inhibitors. Significant increases in atorvastatin concentrations have been reported when given in combination with f-APV and this combination should be used with extreme precaution. Maximum doses of atorvastatin of 20 mg/day in adults is recommended or an alternative HMG-CoA reductase inhibitor, such as fluvastatin or pravastatin, may be used.
- Serious drug interactions could occur between amiodarone, lidocaine, tricyclic antidepressants, quinidine, and warfarin. It is recommended that the concentration of these drugs be monitored when administered concomitantly with APV.
- Coadministering EFV and APV lowers levels of APV 39%. A higher RTV "boost" dose (300 mg per day instead of 100 mg per day) is recommended when EFV is administered with f-APV plus RTV *once* daily. However, no change in the RTV dose is required when EFV is given with f-APV plus RTV *twice* daily.
- f-APV should not be given in combination with LPV/RTV. This combination has resulted in a significant decrease in APV AUC, Cmax, and Cmin and decreases in LPV concentrations as well. Appropriate doses of this combination have not been established.
- IDV and NFV have both been reported to increase APV concentrations. SQV may decrease APV concentrations. Appropriate doses of these combinations have not been established.
- DLV significantly increases APV AUC, Cmax, and Cmin. DLV concentrations are decreased significantly, with AUC decreases of 61%. DLV should not be coadministered with f-APV.
- Coadministration of APV and methadone can decrease plasma levels of methadone. Patients receiving this combination should be closely monitored.
- Coadministration of APV with sildenafil (Viagra) or vardenafil is likely to result in increased PDE5 inhibitor concentrations; patients should be advised that they may be at an increased risk of associated adverse events, including hypotension, visual changes, and priapism.
- The efficacy of hormonal contraceptives may be reduced in patients receiving APV. Alternate or additional methods of birth control should be

coadministered if coadministering APV with hormonal methods of birth control.

- Carbamazepine, phenobarbital, and phenytoin may decrease APV concentration and should be used with caution.
- APV significantly increases ketoconazole and itraconazole concentrations. Dose reduction of ketoconazole and itraconazole may be required for patients receiving this combination.
- APV is a sulfonamide. The potential for cross sensitivity between drugs in the sulfonamide class and APV is unknown. APV should be used with caution in patients with sulfonamide allergy.

Special Instructions

- APV may be taken with or without food.
- Patients taking antacids (or ddI) should take APV at least one hour before or after antacid (or ddI) use.
- APV is primarily metabolized by the liver. Caution should be used when administering APV to patients with impaired hepatic function.

Indinavir *(IDV, Crixivan®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

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

Dosage

Neonatal/Infant dose: Unknown. Due to side effect of hyperbilirubinemia, should not be given to neonates until further information is available.

Pediatric dose: Under study in clinical trials: 500 mg per m^2 of body surface area every eight hours. Patients with small body surface areas may require lower doses (300-400 mg/m^2 every 8 hours).

Adolescent/Adult dose: 800 mg every eight hours.

Combination with ritonavir (adults): IDV 400 mg + RTV 400 mg twice daily, or IDV 800 mg + RTV 200 mg twice daily.

Combination with efavirenz (adults): IDV 1000 mg three times daily + EFV 600 mg once daily.

Major Toxicities

More common: Nausea, abdominal pain, headache, metallic taste, dizziness, and asymptomatic hyperbilirubinemia (10%).

Less common (more severe): Nephrolithiasis (4%) and exacerbation of chronic liver disease. Fat redistribution and lipid abnormalities.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, diabetes, and hemolytic anemia.

Drug Interactions

- Cytochrome P450 3A4 (CYP3A4) responsible for metabolism. There could potentially be multiple drug interactions. [¶]
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- IDV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. IDV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; or sedative-hypnotics (i.e., triazolam or midazolam).
- IDV levels are significantly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin concentrations are increased, therefore a dose reduction of rifabutin to half the usual daily dose is recommended.
- Ketoconazole and itraconazole cause an increase in IDV concentrations (consider reducing adolescent/ adult IDV dose to 600 mg every eight hours).
- Coadministration of clarithromycin increases serum concentration of both drugs (dosing modification not needed).
- Coadministration of NVP or EFV may decrease IDV serum concentration.
- Administration with other PIs: coadministration with NFV increases concentration of both drugs; coadministration with SQV increases concentration of SQV. Should not be coadministered with ATV due to potential for additive hyperbilirubinemia.

[¶] Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. 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 those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer on an empty stomach one hour before or two hours after a meal (or can take with a light meal).
- When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration required to minimize risk of nephrolithiasis (at least 48 oz of fluid daily in adult patients).
- If coadministered with ddI, give at least one hour apart on an empty stomach.
- Decrease dose in patients with hepatic insufficiency.
- Capsules are sensitive to moisture and should be stored in original container with desiccant.

Lopinavir/Ritonavir *(Kaletra™, ABT 378, LPV/RTV)*

URL: **Link to Pediatric Antiretroviral Drug Information**

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

Preparations: Pediatric oral solution: 80 mg lopinavir and 20 mg ritonavir per mL; Capsules: 133.3 mg lopinavir/33.3 mg RTV.

Dosage

Neonatal/Infant dose: No pharmacokinetic data on dosing children less than six months of age.

- For individuals not receiving concomitant nevirapine or efavirenz:

Pediatric dose:

Six months to 12 years of age (without NVP or EFV)	
7 to < 15 kg	12 mg per kg lopinavir/3 mg per kg ritonavir twice daily with food.
15 to 40 kg	10 mg per kg lopinavir/2.5 mg per kg ritonavir twice daily with food.
> 40 kg	400 mg lopinavir/100 mg ritonavir (three capsules or 5 mL) twice daily with food (same as adult dose).

OR

230 mg per m^2 lopinavir/57.5 mg per m^2 ritonavir twice daily with food, up to a maximum of 400 mg lopinavir/100 mg RTV.

Adult/Adolescent dose: 400 mg lopinavir/100 mg ritonavir (three capsules or 5 mL) twice daily with food.

- For individuals receiving concomitant NVP or EFV (which induce lopinavir metabolism, reduce plasma levels and require increased lopinavir/ritonavir dosing) and/or treatment-experienced patients where reduced susceptibility to lopinavir is suspected (such as those with prior treatment with other PIs):

Pediatric dose:

Six months to 12 years of age (with NVP or EFV)	
7 to < 15 kg	13 mg per kg lopinavir/3.25 mg per kg ritonavir twice daily with food.
15 to 50 kg	11 mg per kg lopinavir/2.75 mg per kg ritonavir twice daily with food.
> 50 kg	533 mg lopinavir/133 mg ritonavir (four capsules or 6.5 mL) twice daily with food (same as adult dose).

OR

300 mg per m^2 lopinavir/75 mg per m^2 ritonavir twice daily with food up to a maximum of 533 mg lopinavir/133 mg ritonavir.

Adult/Adolescent dose: 533 mg lopinavir/133 mg ritonavir (four capsules or 6.5 mL) twice daily with food.

Note: Although pediatric clinical trials utilized the mg per m^2 body surface area dosing, the FDA-approved doses are based on a mg per kg body weight dosage. The 230 mg per m^2 lopinavir/57.5 mg per m^2 RTV twice daily regimen without NVP or EFV and the 300 mg per m^2 lopinavir/75 mg per m^2 ritonavir twice daily regimen with concomitant NVP or EFV resulted in lopinavir concentrations similar to those obtained in adults receiving the 400 mg lopinavir/100 mg ritonavir twice daily regimen (without concomitant NVP or EFV). The pediatric trials were done in NNRTI naïve patients and there is little data in heavily pre-treated pediatric patients. In treatment-experienced patients where reduced susceptibility to lopinavir is suspected, higher doses may be required but there is little data to make definitive dosing recommendations at this time.

Major Toxicities

More common: Diarrhea, headache, asthenia, nausea and vomiting, and rash in patients receiving lopinavir/ritonavir with other antiretroviral drugs.

Less common (more severe): Fat redistribution and lipid abnormalities.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

Drug Interactions

- Lopinavir/ritonavir is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.*
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Drugs that should not be coadministered with lopinavir/ritonavir include: antiarrhythmics (i.e., flecainide, propafenone); cisapride; neuroleptics (i.e., pimozide); ergot alkaloid derivatives; antihistamines (i.e., astemizole, terfenadine); sedative-hypnotics (i.e., midazolam, triazolam); HMG-COA reductase inhibitors (i.e., lovastatin, simvastatin); rifampin and St. John's wort.
- EFV and NVP induce the metabolism of lopinavir and decrease plasma concentrations. A dose increase of lopinavir/ritonavir is recommended (see dosage section).
- Anticonvulsant drugs including carbamazepine, phenytoin, and phenobarbital increase CYP3A activity, leading to increased clearance and, therefore, lower levels of lopinavir, and should be used with caution.
- Dexamethasone decreases lopinavir serum concentrations. Use with caution.
- Lopinavir/ritonavir increases serum concentrations of some HMG-CoA reductase inhibitors (i.e., atorvastatin). Pravastatin and fluvastatin are preferred alternative agents.
- Lopinavir/ritonavir increases serum clarithromycin concentration and clarithromycin dose adjustment is recommended in patients with impaired renal function (CrCl 30-60 mL/min decrease clarithromycin dose by 50%; CrCl <30 mL/min decrease clarithromycin dose by 75%).
- Lopinavir/ritonavir increases rifabutin and rifabutin metabolite concentrations, and dose reduction of rifabutin by at least 75% of the usual dose is recommended.
- Lopinavir/ritonavir increases sildenafil (Viagra) serum concentrations. Reduce dose of sildenafil and monitor for toxicity.
- Lopinavir/ritonavir increases serum concentrations of the antiarrhythmics amiodarone, bepridil, lidocaine (systemic) and quinidine. Monitoring of antiarrhythmic serum concentrations is recommended.
- Lopinavir/ritonavir may increase serum concentrations of the immunosuppressant agents cyclosporine, tacrolimus, and rapamycin. Monitor serum concentrations of these agents when coadministered.
- Lopinavir/ritonavir increases serum concentrations of dihydropyridine calcium channel blockers (i.e., felodipine, nifedipine, nicardipine). Clinical monitoring is recommended.
- Lopinavir/ritonavir decreases methadone serum concentrations when coadministered. Patients should be closely monitored for withdrawal symptoms, and methadone dosage should be increased as necessary.
- Lopinavir/ritonavir increases serum concentrations of ketoconazole and itraconazole. High doses of these agents (>200 mg/day) are not recommended.
- Lopinavir/ritonavir decreases atovaquone concentrations. The clinical significance is unknown.
- Ethinyl estradiol levels are reduced by lopinavir/ritonavir, and alternative or additional methods of birth control should be used if coadministered with hormonal methods of birth control.
- Administration with other PIs: appropriate doses of lopinavir/ritonavir with APV, ATV, SQV, IDV, or additional RTV have not been established.
- Lopinavir/ritonavir oral solution contains 42.4% alcohol and can cause a disulfiram-like reaction when coadministered with disulfiram or metronidazole.

Special Instructions

- Administer with food. High fat meal increases absorption, especially of the liquid preparation.
- If coadministered with ddI, ddI should be given one hour before or two hours after lopinavir/ritonavir.
- Oral solution and capsules should be refrigerated. Can be kept at room temperature up to 77ºF (25ºC) if used within two months.

* Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions with multiple drugs, some of which 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 those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Nelfinavir *(NFV, Viracept®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Powder for oral suspension: 50 mg per one level gram scoop full (200 mg per one level teaspoon); *Tablets:* 250 mg tablet.

Dosage

Neonatal/Infant dose: Under study in Pediatric AIDS Clinical Trials Group protocol 353: 40 mg per kg of body weight every 12 hours.

Pediatric dose: Currently under review: 20 to 30 mg per kg of body weight three times a day is the FDA approved dose. However, doses as high as 45 mg/kg every 8 hours are routinely used. Twice daily dosing in pediatric patients is under study (50-55 mg/kg/dose) in older children (>6 years of age).

Adolescent/Adult dose: 1250 mg (5 tablets) twice daily or 750 mg (3 tablets) three times daily. Doses of 1500 mg (6 tablets) twice daily are under study in adults.

Major Toxicities

More common: Diarrhea.

Less common: Asthenia, abdominal pain, rash, and exacerbation of chronic liver disease. Fat redistribution and lipid abnormalities.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, and diabetes.

Drug Interactions

- NFV is in part metabolized by cytochrome P450 3A4 (CYP3A4). There could potentially be multiple drug interactions.*
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- NFV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. NFV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (i.e., quinidine or amiodarone); or sedative-hypnotics (i.e., triazolam or midazolam).
- NFV levels are greatly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin causes less decline in NFV concentrations; if coadministered with NFV, rifabutin should be reduced to one half the usual dose.
- Estradiol levels are reduced by NFV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- Coadministration with DLV increases NFV concentrations twofold and decreases DLV concentrations by 50%. There are no data on coadministration with NVP, but some experts use higher doses of NFV if used in combination with NVP.
- Administration with other PIs: coadministration with IDV increases concentration of both drugs; coadministration with SQV increases concentration of SQV with little change in NFV concentration; coadministration with RTV increases concentration of NFV without change in RTV concentration. No data on coadministration with ATV.

Special Instructions

- Administer with meal or light snack.
- If coadministered with ddI, NFV should be administered two hours before or one hour after ddI.
- For oral solution: powder may be mixed with water, milk, pudding, ice cream, or formula (for up to six 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.
- Tablets readily dissolve in water and produce a dispersion that can be mixed with milk or chocolate milk; tablets also can be crushed and administered with pudding.

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Ritonavir *(RTV, Norvir®)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Oral solution: 80 mg/mL; *Capsules:* 100 mg

Dosage

Neonatal/Infant dose: Under study in Pediatric AIDS Clinical Trials Group protocol 354 (single dose pharmacokinetics).

Pediatric usual dose: 400 mg per m^2 of body surface area every 12 hours. To minimize nausea/vomiting, initiate therapy starting at 250 mg per m^2 of body surface area every 12 hours and increase stepwise to full dose over five days as tolerated.

Pediatric dosage range: 350 to 400 mg per m^2 of body surface area every 12 hours.

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 five days as tolerated.

Combination with saquinavir (Fortovase) (adults): RTV 400-600 mg + SQV 400 mg twice daily.

Pharmacokinetic Enhancer: Used at lower doses as pharmacokinetic enhancer of other protease inhibitors. Doses most commonly used in adults are 200 mg every 12 hours to 400 mg every 12 hours when combined with other protease inhibitors.

Major Toxicities

More common: Nausea, vomiting, diarrhea, headache, abdominal pain, and anorexia.

Less common: Circumoral paresthesias and increase in liver enzymes. Fat redistribution and lipid abnormalities.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

Drug Interactions

- RTV is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Not recommended for concurrent use with analgesics (i.e., meperidine, piroxicam, or propoxyphene); antihistamines (i.e., astemizole or terfenadine); certain cardiac drugs (i.e., amiodarone, bepridil hydrochloride, flecainide acetate, propafenone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (i.e., alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, or zolpidem); certain psychotropic drugs (i.e., bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin.
- Estradiol levels are reduced by RTV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- RTV increases metabolism of theophylline (levels should be monitored, and dose may need to be increased).
- RTV increases levels of clarithromycin (dose adjustment may be necessary in patients with impaired renal function); desipramine (dose adjustment may be necessary); and warfarin (monitoring of anticoagulant effect is necessary).
- RTV may increase or decrease digoxin levels (monitoring of levels is recommended).
- Drugs that increase CYP3A activity can lead to increased clearance and, therefore, lower levels of RTV include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because RTV can affect the metabolism of these drugs as well).
- Administration with other PIs: coadministration with ATV, SQV and NFV increases concentration of these drugs with little change in RTV concentration.

Special Instructions

- Administration with food increases absorption and helps decrease gastrointestinal side effects.
- If RTV is prescribed with ddI, there should be two hours between taking each of the drugs.

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- Oral solution should be kept at room temperature (66-77ºF); do not refrigerate. Shake well before each use.
- Soft gel capsules are recommended to be refrigerated, but can be kept at room temperature if used within 30 days and stored below 77ºF.
- To minimize nausea, therapy should be initiated at a low dose and increased to full dose over five days as tolerated.
- Techniques to increase tolerance in children:
  a. mixing oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream;
  b. dulling the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates;
  c. coating the mouth by giving peanut butter to eat before the dose; or
  d. administration of strong-tasting foods such as maple syrup, cheese, or strong-flavored chewing gum immediately after dose.

Saquinavir *(SQV, Invirase ™hard gel capsule and Fortovase ™soft gel capsule)*

URL: **Link to Pediatric Antiretroviral Drug Information**

Preparations: Soft gel capsules: 200 mg (preferred product); Hard gel capsules*:* 200 mg. Please note that Saquinavir-HGC (Invirase) is not recommended except in combination with ritonavir.

Dosage

Neonatal/Infant dose: Unknown.

Pediatric dose: Under study: 50 mg per kg body weight every 8 hours as single protease inhibitor therapy. 33 mg per kg body weight every 8 hours as usual therapy with nelfinavir.
Adolescent/Adult dose: Soft gel capsules: 1200 mg three times a day or 1600 mg twice daily.

Major Toxicities

More common: Diarrhea, abdominal discomfort, headache, nausea, paresthesias, and skin rash.

Less common: Exacerbation of chronic liver disease. Fat redistribution and lipid abnormalities.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, and diabetes.

Drug Interactions

- SQV is metabolized by the cytochrome P450 3A4 (CYP3A4) system in the liver, and there are numerous potential drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- SQV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. SQV is not recommended for concurrent use with antihistamines (i.e., astemizole or terfenadine); cisapride; ergot alkaloid derivatives, or sedative-hypnotics (i.e., midazolam or triazolam).
- SQV levels are significantly reduced with concurrent use of rifampin (decreases SQV levels by 80%), rifabutin (decreases SQV levels by 40%), and NVP (decreases SQV levels by 25%).
- SQV levels are decreased by carbamazepine, dexamethasone, phenobarbital, and phenytoin.
- SQV levels are increased by DLV and ketoconazole.
- SQV may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be closely monitored for toxicity.
- Administration with other PIs: coadministration with ATV, IDV, RTV, or NFV increases concentration of SQV with little change in concentration of the other drug.

Special Instructions

- Administer within two hours of a full meal to increase absorption.
- Concurrent administration of grapefruit juice increases SQV concentration.
- Sun exposure can cause photosensitivity reactions; therefore, sunscreen or protective clothing is recommended.
- Fortovase® and Invirase® are not bioequivalent and cannot be used interchangeably. Fortovase® is the recommended formulation.

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Fusion Inhibitors

Enfuvirtide *(Fuzeon™, T-20)*

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

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

Dosage
Neonatal/Infant dose: Not approved for use in pediatric patients below the age of 6 years old.

Pediatric/adolescent dose (6-16 years of age):
2 mg/kg twice daily, maximum dose 90 mg (1mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

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

Major Toxicities
Most common: Almost all patients (98%) get 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.

Less common: Increased rate of bacterial pneumonia (unclear association).

Rare: Hypersensitivity reactions including fever, nausea and vomiting, chills, vigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillan-Barre syndrome. Patients experiencing hypersensitivity reactions should seek immediate medical attention. Therapy should not be restarted following 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.
- Once reconstituted, Fuzeon should be injected immediately or kept refrigerated in the original vial until use. Reconstituted Fuzeon must be used within 24 hours.
- 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.
- 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.

References

1. Working Group on Antiretroviral Therapy: National Pediatric HIV Resource Center. Antiretroviral therapy and medical management of the human immunodeficiency virus-infected child. *Pediatr Infect Dis*, 1993. 12(6):513-22.
2. Perelson AS, Neumann AU, Markowitz M, et al. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science*, 1996. 271(5255):1582-6.
3. Havlir DV, Richman DD. Viral dynamics of HIV: implications for drug development and therapeutic strategies. *Ann Intern Med*, 1996. 124(11):984-94.
4. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*, 1994. 331(18):1173-80.
5. Centers for Disease Control and Prevention. Guidelines for using antiretroviral agents in HIV-infected adults and adolescents. *MMWR*, 2002. 51(RR-7):1-56. (**http://AIDSinfo.nih.gov** - see this Web site for most updated guidelines).
6. Centers for Disease Control and Prevention. USPHS Task Force Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. *MMWR*, 2002. 51(RR-18):1-38. (**http://AIDSinfo.nih.gov** - see this Web site for most updated guidelines).
7. Centers for Disease Control and Prevention. Recommendations of the U.S. Public Health Service Task Force on use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. *MMWR*, 1994. 43(RR-11):1-20.
8. Center for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in pediatric HIV infection. *MMWR*, 1998. 47(RR-4):1-38.
9. Working Group on Antiretroviral Therapy and Medical Management of Infants. Antiretroviral therapy and medical management of pediatric HIV infection and 1997 USPHS/IDSA report on the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Pediatrics*, 1998. 102(4 Pt 2):999-1085.
10. Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral and revised recommendations for HIV screening of pregnant women. *MMWR*, 2001. 50(RR-19):1-110.
11. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. *Pediatrics*, 2000. 106(6):E88.
12. American College of Obstetricians and Gynecologists. Human immunodeficiency virus infections in pregnancy. *Int J Gynaecol Obstet*, 1997. 57(1):73-80.
13. American Academy of Pediatrics, Committee on Pediatric AIDS. Human milk, breastfeeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*, 1995. 96(5 Pt 1):977-9.
14. Centers for Disease Control and Prevention. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *MMWR*, 1995. 44(RR-4).
15. State of New York Department of Health Memorandum No. AI 99-01 "Maternal-Pediatric HIV Prevention and Care Program: HIV counseling and voluntary testing of pregnant women; routine HIV testing of newborns".
16. Dunn DT, Brandt CD, Kirvine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS*, 1995. 9(9):F7-11.
17. Steketee RW, Abrams EJ, Thea DM, et al. Early detection of perinatal human immunodeficiency virus (HIV) type 1 infection using HIV RNA amplification and detection. New York City Perinatal HIV Transmission Collaborative Study. *J Infect Dis*, 1997. 175(3):707-11.
18. Delamare C, Burgard M, Mayaux MJ, et al. HIV-1 RNA detection in plasma for the diagnosis of infection in neonates. The French Pediatric HIV Infection Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1997. 15(2):121-5.
19. Simonds RJ, Brown TM, Thea DM, et al. Sensitivity and specificity of a qualitative RNA detection assay to diagnose HIV infection in young infants. Perinatal AIDS Collaborative Transmission Study. *AIDS*, 1998. 12(12):1545-9.
20. Cunningham CK, Charbonneau TT, Song K, et al. Comparison of human immunodeficiency virus 1 DNA polymerase chain reaction and qualitative and quantitative RNA polymerase chain reaction in human immunodeficiency virus 1-exposed infants. *Ped Infect Dis J*, 1999. 18(1):30-5.
21. Young NL, Shaffer N, Chaowanachan T, et al. Early diagnosis of HIV-1-infected infants in Thailand using RNA and DNA PCR assays sensitive to non-B subtypes. *J Acquir Immune Defic Syndr*, 2000. 24(5):401-7.
22. Nesheim S, Palumbo P, Sullivan K, et al. Quantitative RNA testing for diagnosis of HIV-infected infants. *J Acquir Immune Defic Syndr*, 2003. 32(2):192-5.
23. McIntosh K, Pitt J, Brambilla D, et al. Blood culture in the first 6 months of life for the

diagnosis of vertically transmitted human immunodeficiency virus infection. The Women and Infants Transmission Study Group. *J Infect Dis*, 1994. 170(4):996-1000.

24. Nesheim S, Lee F, Kalish ML, et al. Diagnosis of perinatal human immunodeficiency virus infection by polymerase chain reaction and p24 antigen detection after immune complex dissociation in an urban community hospital. *J Infect Dis*, 1997. 175(6):1333-6.
25. Bryson YJ, Luzuriaga K, Sullivan JL, Wara DW. Proposed definitions for in utero versus intrapartum transmission of HIV-1. *N Engl J Med*, 1992. 327(17):1246-7.
26. Mayaux MJ, Burgard M, Teglas JP, et al. Neonatal characteristics in rapidly progressive perinatally acquired HIV-1 disease. The French Pediatric HIV Infection Study Group. *JAMA*, 1996. 275(8):606-10.
27. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and Infants Transmission Study Group. *N Engl J Med*, 1997. 336(19):1337-42.
28. Kovacs A, Xu J, Rasheed S, et al. Comparison of a rapid nonisotopic polymerase chain reaction assay with four commonly used methods for the early diagnosis of human immunodeficiency virus type 1 infection in neonates and children. *Pediatr Infect Dis J*, 1995. 14(11):948-54.
29. Centers for Disease Control and Prevention. Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. *MMWR*, 1999. 48(RR-13):1-27, 29-31.
30. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. *J Infec Dis*, 1996. 174(1):244-5.
31. Kline NE, Schwarzwald H, Kline MW. False Negative DNA Polymerase Chain Reaction In An Infant With Subtype C HIV-1 Infection. *Pediatr Infect Dis J*, 2002. 21(9):885-6.
32. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis*, 2002. 34(3):417-8.
33. Triques K, Coste J, Perret JL, et al. Efficiencies of four versions of the AMPLICOR HIV-1 MONITOR test for quantification of different subtypes of human immunodeficiency virus type 1. *J Clin Microbiol*, 1999. 37(1):110-6.
34. Antunes R, Figueiredo S, Bartolo I, et al. Evaluation of the clinical sensitivities of three viral load assays with plasma samples from a pediatric population predominantly infected with human immunodeficiency virus type 1 subtype G and BG recombinant forms. *J Clin Microbiol*, 2003. 41(7):3361-7.
35. Plantier JC, Gueudin M, Damond F, et al. Plasma RNA quantification and HIV-1 divergent strains. *J Acquir Immune Defic Syndr*, 2003. 33(1):1-7.
36. Geelen S, Lange J, Borleffs J, et al. Failure to detect a non-B HIV-1 subtype by the HIV-1 Amplicor Monitor test, version 1.5: a case of unexpected vertical transmission. *AIDS*, 2003. 17(5):781-2.
37. Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: The pediatric AIDS clinical trials group P1009 study. *J Allergy Clin Immunol*, 2003. 112(3):973-80.
38. European Collaborative Study. Age-related standards for T lymphocyte subsets based on uninfected children born to human immunodeficiency virus 1-infected women. The European Collaborative Study. *Pediatr Infect Dis J*, 1992. 11(12):1018-26.
39. 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(RR-12):1-10.
40. El-Sadar W, Oleske JM, Agins BD, et al. Evaluation and management of early HIV infection. Clinical Practice Guideline No. 7 (AHCPR Publication No. 94-0572). Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, 1994.
41. Wilfert CM, Gross PA, Kaplan JE, et al. Quality standard for the enumeration of CD4+ lymphocytes in infants and children exposed to or infected with human immunodeficiency virus. *Clin Infect Dis*, 1995. 21(Suppl 1):S134-5.
42. Kourtis AP, Ibegbu C, Nahmias AJ, et al. Early progression of disease in HIV-infected infants with thymus dysfunction. *N Engl J Med*, 1996. 335(19):1431-6.
43. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet*, 2003. 362(9396):1605-11.
44. Katzenstein TL, Pedersen C, Nielsen C, et al. Longitudinal serum HIV RNA quantification: correlation to viral phenotype at seroconversion and clinical outcome. *AIDS*, 1996. 10(2):167-73.
45. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. *JAMA*, 1995. 274(7):554-8.

46. Mellors JW, Kingsley LA, Rinaldo CR, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med*, 1995. 122(8):573-9.
47. Clementi M, Menzo S, Bagnarelli P, et al. Clinical use of quantitative molecular methods in studying human immunodeficiency virus type 1 infection. *Clin Microbiol Rev*, 1996. 9(2):135-47.
48. Palumbo PE, Kwok SH, Waters S, et al. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. *J Pediatr*, 1995. 126(4):592-5.
49. Abrams EJ, Weedon J, Steketee RW, et al. Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants. New York City Perinatal HIV Transmission Collaborative Study Group. *J Infec Dis*, 1998. 178(1):101-8.
50. McIntosh K, Shevitz A, Zaknun D, et al. Age- and time-related changes in extracellular viral load in children vertically infected by human immunodeficiency virus. *Pediatr Infect Dis J*, 1996. 15(12):1087-91.
51. 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. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Infect Dis*, 1997. 175(5):1029-38.
52. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA*, 1998. 279(10):756-61.
53. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*, 1997. 126(12):946-54.
54. O'Brien WA, Hartigan PM, Daar ES, et al. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. VA Cooperative Study Group on AIDS. *Ann Intern Med*, 1997. 126(12):939-45.
55. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med*, 1997. 126(12):929-38.
56. Reichelderfer PS, Coombs RW. Virologic parameters as surrogate markers for clinical outcome in HIV-1 disease: verification, variation, and validation. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995. 10(Suppl 2):S19-24.
57. Goetz MB, Moatamed F, Howanitz JH. Measurement of plasma HIV viral load (VL) by bDNA versus RT PCR (PCR) assays. *Clin Infect Dis*, 1997. 25:394. (Abstract 207).
58. Brambilla D, Leung S, Lew J, et al. Absolute copy number and relative change in determinations of human immunodeficiency virus type 1 RNA in plasma: effect of an external standard on kit comparisons. *J Clin Microbiol*, 1998. 36(1):311-4.
59. Vandamme AM, Schmit JC, Van Dooren S, et al. Quantification of HIV-1 RNA in plasma: comparable results with the NASBA HIV-1 RNA QT and the AMPLICOR HIV monitor test. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1996. 13(2):127-39.
60. Raboud JM, Montaner JSG, Conway B, et al. Variation in plasma RNA levels, CD4 cell counts, and p24 antigen levels in clinically stable men with human immunodeficiency virus infection. *J Infect Dis*, 1996. 174(1):191-4.
61. Grubman S, Gross E, Lerner-Weiss N, et al. Older children and adolescents living with perinatally acquired human immunodeficiency virus infection. *Pediatrics*, 1995. 95(5):657-63.
62. Schneider MB. Physical examination. In: Friedman SB, Fisher MM, Schoenberg SK, Alderman EM (eds). Comprehensive adolescent health care. 2nd ed. St. Louis, MO: Mosby-Year Book, Inc., 1998. p. 69-80.
63. Rogers A (ed). Pharmacokinetics and pharmacodynamics in adolescents. *J Adolesc Health*, 1994. 15:605-78.
64. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*, 2000. 133(1):21-30.
65. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics*, 2002. 109(4):e61.
66. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J.*, 1999. 18(8):682-9.
67. Howard AA, Arnsten JH, Lo Y, et al. prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS*, 2002. 16(16):2175-82.
68. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J.*, 2000. 19(12):1148-53.
69. Katko E, Johnson GM, Fowler SL, Turner RB. Assessment of adherence with medications in

human immunodeficiency virus-infected children. *Pediatr Infect Dis J*, 2001. 20(12):1174-6.

70. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *Am J Hosp Pharm*, 1991. 48(9):1978-88.
71. Dolezal C, Mellins C, Brackis-Cott E, Abrams EJ. The reliability of reports of medical adherence from children with HIV and their adult caregivers. *J Pediatr Psychol*, 2003. 28(5):355-61.
72. Gigliotti F, Murante BL, Weinberg GA. Short course directly observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Ped Infect Dis J*, 2001. 20(7):716-8.
73. Van Rossum AM, Bergshoeff AS, Fraaij PL, et al. Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*, 2002. 21(8):743-7.
74. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet*, 1996. 348(9024):383-6.
75. Wu AW, Ammassari A, Antinori A. Adherence to antiretroviral therapy: where are we, and where do we go from here? *J Acquir Immune Defic Syndr*, 2002. 31(Suppl 3):S95-7.
76. Czyzewski DI, Runyan D, Lopez MA, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader*, 2000. 10(2):88-94.
77. AIDS Institute New York State Department of Health. Promoting adherence to HIV antiretroviral therapy. Available at **www.hivguidelines.org/public_html/center/best-practices/treatment_adherence/pdf/treat_adherence_full.pdf**.
78. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics*, 2000. 105(6):E80.
79. Reynolds E, Berrien V, Acosta-Glynn C, Salazar JC. Home based, intense, nursing intervention trial improves adherence to HAART in HIV infected children. Pediatric Academic Societies Annual Meeting, Baltimore, MD. April 28-May 1, 2001 (Abstract#1441).
80. Mitty JA, Stone VE, Sands M, et al. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress. *Clin Infect Dis*, 2002. 34(7):984-90.
81. Belzer ME, Fuchs DN, Luftman GS, Tucker DJ. Antiretroviral adherence issues among HIV-positive adolescents and young adults. *J Adolesc Health*, 1999. 25(3):316-9.
82. Rogers AS, Miller S, Murphy DA, et al. The TREAT (Therapeutic Regimens Enhancing Adherence in Teens) program: theory and preliminary results. *J Adolesc Health*, 2001. 29(3 Suppl):30-8.
83. Lyon ME, Trexler C, Akpan-Townsend C et al. A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project. *AIDS Patient Care STDS*, 2003. 17(6):299-308.
84. AIDS Institute New York State Department of Health. Supportive Care Issues for Children with HIV Infection, 2001:18-1-18-22. Available at **http://www.hivguidelines.org/public_html/center/clinical-guidelines/ped_adolescent_hiv_guidelines/html/peds_supportive_care/pdf/supportive_care.pdf**
85. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med*, 1988. 319(14):889-96.
86. McKinney RE, Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med*, 1991. 324(15):1018-25.
87. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med*, 1991. 324(3):137-44.
88. Lewis LL, Venzon D, Church J, et al. Lamivudine in children with human immunodeficiency virus infection: a phase I/II study. The National Cancer Institute Pediatric Branch-Human Immunodeficiency Virus Working Group. *J Infect Dis*, 1996. 174(1):16-25.
89. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics*, 1995. 96(2 Pt 1):247-52.
90. Kline MW, Culnane M, Van Dyke RB, et al. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. AIDS Clinical Trials Group 240 Team. *Pediatrics*, 1998. 101(2):214-20.
91. McKinney RE, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naïve HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr*, 1998. 133(4):500-8.
92. Paediatric European Network for Treatment of AIDS (PENTA). A randomized double-blind trial of the addition of lamivudine or matching placebo to current nucleoside analogue reverse transcriptase inhibitor therapy in HIV-infected

children: the PENTA-4 trial. *AIDS*, 1998. 12(14):F151-60.

93. Nachman S, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*, 2000. 283(4):492-8.
94. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*, 1997. 336(19):1343-9.
95. Yogev R, Lee S, Wiznia A, et al. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J*, 2002. 21(2):119-25.
96. Gortmaker S, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*, 2001. 345(21):1522-8.
97. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*, 2000. 284(2):190-7.
98. Paediatric European Network for Treatment of AIDS (PENTA). Five year follow up of vertically HIV infected children in a randomised double blind controlled trial of immediate versus deferred zidovudine: the PENTA 1 trial. *Arch Dis Child*, 2001. 84(3):230-6.
99. Gray L, Newell ML, Thorne C, et al. Fluctuations in symptoms in human immunodeficiency virus-infected children: the first 10 years of life. *Pediatrics*, 2001. 108(1):116-22.
100. Leonard EG, McComsey GA. Metabolic complications of antiretroviral therapy in children. *Ped Infect Dis J*, 2003. 22(1):77-84.
101. Amaya RA, Kozinetz CA, McMeans A, et al. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis*, 2002. 21(5):405-10.
102. Idemyor V. Continuing debate over HIV therapy initiation. *HIV Clin Trials*, 2002. 3(2):173-6.
103. Abrams EJ, Wiener J, Carter R, et al. Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children. *AIDS*, 2003. 17(6):867-77.
104. Luzuriaga K, McManus M, Catalina M, et al. Early therapy of vertical human immunodeficiency virus type 1 (HIV-1) infection: control of viral replication and absence of persistent HIV-1-specific immune responses. *J Virol*, 2000. 74(15):6984-91.
105. Chadwick EG, Palumbo P, Rodman J, et al. Early therapy with ritonavir (RTV), ZDV and 3TC in HIV-1-infected children 1-24 months of age. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL, 2001. (Abstract 677).
106. Luzuriaga K, Wu H, McManus M, et al. Dynamics of human immunodeficiency virus type 1 replication in vertically infected infants. *J Virol*, 1999. 73(1):362-7.
107. Hainaut M, Peltier CA, Gerard M, et al. Effectiveness of antiretroviral therapy initiated before the age of 2 months in infants vertically infected with human immunodeficiency virus type 1. *Europ J Pediatr*, 2000. 159(10):778-82.
108. Faye A, Bertone C, Teglas JP, et al. Early multitherapy including a protease inhibitor for human immunodeficiency virus type 1-infected infants. *Pediatr Infect Dis J*, 2002. 21(6):518-25.
109. Pomerantz RJ. Residual HIV-1 infection during antiretroviral therapy: the challenge of viral persistence. *AIDS*, 2001. 15(10):1201-11.
110. Zhang J, Crumpacker CS. Human immunodeficiency virus type 1 RNA in peripheral blood mononuclear cells of patients receiving prolonged highly active antiretroviral therapy. *J Infec Dis*, 2001. 184(10):1341-4.
111. Frenkel LM, Wang Y, Learn GH, et al. Multiple viral genetic analyses detect low-level human immunodeficiency virus type 1 replication during effective highly active antiretroviral therapy. *J Virol*, 2003. 77(10):5721-30.
112. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Ped Infect Dis J*, 2001. 20(8):746-51.
113. Galli L, de Martino M, Tovo PA, et al. Predictive value of the HIV paediatric classification system for the long-term course of perinatally infected children. *Int J Epidemiol*, 2000. 29(3):573-8.
114. Eastman PS, Shapiro DE, Coombs RW, et al. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in pediatric AIDS Clinical Trials Group Protocol 076. *J Infect Dis*, 1998. 177(3):557-64.
115. McSherry GD, Shapiro DE, Coombs RW, et al. The effects of zidovudine in the subset of infants infected with human immunodeficiency virus type-1 (Pediatric AIDS Clinical Trials Group Protocol 076). *J Pediatr*, 1999. 134(6):717-24.
116. Stiehm ER, Lambert JS, Mofenson LM, et al. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV

transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group protocol 185. *J Infect Dis*, 1999. 179(3):567-75.

117. Parker MM, Wade N, Lloyd RM Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *JAIDS*, 2003. 32(3):292-7.

118. Grant RM, Hecht FM, Warmerdam M, et al. Time trends in primary HIV-1 drug resistance among recently infected persons. *JAMA*, 2002. 288(2):181-8.

119. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med*, 2002. 347(6):385-94.

120. Hirsch MS, Brun-Vezinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAMA*, 2000. 283(18):2417-26.

121. Englund J, Baker C, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*, 1997. 336(24):1704-12.

122. Kline MW, van Dyke RB, Lindsey J, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics*, 1999. 103(5):e62.

123. Bakshi S, Britto P, Capparelli E, et al. Evaluation of pharmacokinetics, safety, tolerance, and activity of combination of zalcitabine and zidovudine in stable, zidovudine-treated pediatric patients with human immunodeficiency virus infection. AIDS Clinical Trials Group Protocol 190 Team. *J Infect Dis*, 1997. 175(5):1039-50.

124. Kline MW, Blanchard S, Fletcher CV, et al. A phase I study of abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. AIDS Clinical Trials Group 330 Team. *Pediatrics*, 1999. 103(4):e47.

125. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*, 2002. 359(9308):733-40.

126. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. *AIDS*, 1999. 13(8):999-1000.

127. Frissen PHJ, de Vries J, Weigel HM, Brinkman K. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity. *AIDS* 2001;15(2):289.

128. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials*, 2002. 3(1):9-16.

129. Robbins G, Shafer R, Smeaton L, et al. Antiretroviral strategies in naïve HIV subjects: comparisons of sequential 3-drug regimens (ACTG 384). XIV International AIDS Conference, Barcelona, Spain, July 7-14, 2002 (Abs. LbOr20A).

130. Blanco F, Garcia-Benayas T, Jose de la Cruz J, et al. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials*, 2003. 4(1):11-19.

131. GlaxoSmithKline. Dear Health Care Professional Letter. September 2003 (access: **http://www.gsk.ca/en/health_info/hiv_eng_dhcl.pdf**).

132. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*, 2002. 21(7):659-63.

133. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*, 1999. 354(9181):795-802.

134. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*, 1999. 341(25):1874-81.

135. Staszewski S, Morales-Ramirez J, Tashima K, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med*, 1999. 341(25):1865-73.

136. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*, 2003. 17(7):987-99.

137. Bartlett J, on behalf of the FTD-302 Study Investigators and the FTC-302 Independent Steering Committee. Severe liver toxicity in patients receiving two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor. 8th Conference on Retroviruses and Opportunistic Infections. Chicago, IL, 2001. (Abstract 19).

138. Centers for Disease Control and Prevention. Serious adverse events attributed to nevirapine regimens for post-exposure prophylaxis after HIV exposures - worldwide, 1997-2000. *MMWR*, 2001. 49(51):1153-6.

139. Mueller BU, Nelson RP Jr, Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*, 1998. 101(3 Pt 1):335-43.
140. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis*, 1999. 28(5):1109-18.
141. van Rossum AM, Niesters HG, Geelen SP, et al. Clinical and virologic response to combination treatment with indinavir, zidovudine, and lamivudine in children with human immunodeficiency virus-1 infection: a multicenter study in the Netherlands. On behalf of the Dutch Study Group for Children with HIV-1 infections. *J Pediatr*. 136(6):780-8.
142. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*, 2002. 34(7):991-1001.
143. Bristol-Myers Squibb. Dear Health Care Provider Letter. August 8, 2003 (access: **http://www.fda.gov/oashi/aids/new.html#rey**).
144. Raines CP, Flexner C, Sun E, et al. Safety, tolerability, and antiretroviral effects of ritonavir-nelfinavir combination therapy administered for 48 weeks. *J Acquir Immune Defic Syndr*, 2000. 25(4):322-8.
145. Katzenstein TL, Kirk O, Pedersen C, et al. The Danish protease inhibitor study: a randomized study comparing the virological efficacy of 3 protease inhibitor-containing regimens for the treatment of human immunodeficiency virus type 1 infection. *J Infect Dis*, 2000. 182(3):744-50.
146. Paredes R, Puig T, Arno A, et al. High-dose saquinavir plus ritonavir: long-term efficacy in HIV-positive protease inhibitor-experienced patients and predictors of virologic response. *J Acquir Immune Defic Syndr*, 1999. 22(2):132-8.
147. Rockstroh JK, Bergmann F, Wiesel W, et al. Efficacy and safety of twice daily first-line ritonavir/indinavir plus double nucleoside combination therapy in HIV-infected individuals. German Ritonavir/Indinavir Study Group. *AIDS*, 2000. 14(9):1181-5.
148. Grub S, Delora P, Ludin E, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther*, 2003. 71(3):122-30.
149. Hoffmann F, Notheis G, Wintergerst U, et al. Comparison of ritonavir plus saquinavir- and nelfinavir plus saquinavir-containing regimens as salvage therapy in children with human immunodeficiency type 1 infection. *Pediatr Infect Dis J*, 2000. 19(1):47-51.
150. Kline MW, Brundage RC, Fletcher CV, et al. Combination therapy with saquinavir soft gelatin capsules in children with human immunodeficiency virus infection. *Pediatr Infect Dis J*, 2001. 20(7):666-71.
151. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J*, 2002. 21(7):653-9.
152. Church JA, Hughes M, Chen J, et al. for the Pediatric AIDS Clinical Trials Group P1005 Study Team. Long-term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J*, 2004. 23(8):713-8.
153. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*, 2003. 22(3):216-24.
154. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*, 2000. 16(12):1113-21.
155. Funk MB, Linde R, Wintergerst U, et al. Preliminary experiences with triple therapy including nelfinavir and two reverse transcriptase inhibitors in previously untreated HIV-infected children. *AIDS*, 1999. 13(13):1653-8.
156. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics*, 2002. 110 (2 pt 1):e19.
157. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in Dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis*, 2002. 34(7):1008-16.
158. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infec Dis*, 2001. 183(7):1116-20.
159. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naïve Antiretrovirals (I.Co.N.A.) study. *J Infect Dis*, 2002. 185(8):1062-9.
160. Nunez M, Soriano V, Martin-Carbonero L, et al. The SENC trial: a randomized, open-label study

comparing efavirenz versus nevirapine: results at 48 weeks. XIV International AIDS Conference, Barcelona, Spain, July 7-12, 2002 (Abstract TuPeB4441).

161. van Leth F, Hassink E, Phanuphak P, et al. The 2NN study: a randomized comparative open label trial of first-line antiretroviral therapy with regimens containing either nevirapine, efavirenz, or both drugs combined in addition to stavudine and lamivudine. 10th Conference on Retroviruses and Opportunistic Infections. Boston, MA, February 10-14, 2003 (Abstract 176).

162. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*, 2002. 35(1):182-9.

163. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults: A randomized equivalence trial. *JAMA*, 2001. 285(9):1155-63.

164. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*, 2001. 107(1):E4.

165. Saavedra J, McCoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, September 22-25, 2001 (Abstract 1941).

166. Wells CJ, Sharland M, Smith CJ, et al. Triple nucleoside analogue therapy with zidovudine (AZT), lamivudine (3TC), and abacavir (ABC) in the paediatric HIV London South Network (PHILS-NET) cohort. XIV International AIDS Conference. Barcelona, Spain, July 7-12, 2002 (Abstract TuPeB4625).

167. Hughes W, McDowell JA, Shenep J, et al. Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. *Antimicrobial Agents Chemother*, 1999. 43(3):609-15.

168. National Institute of Allergy and Infectious Diseases. Important interim results from a phase III, randomized, double-blind comparison of three protease inhibitor-sparing regimens for initial treatment of HIV infection (AACTG protocol 5095). March 13, 2003. Available at: **http://www.nlm.nih.gov/databases/alerts/hiv.html**.

169. Moyle GJ. Where now for Trizivir? Role of the triple-NRTI pill post-ACTG 5095. *AIDS Read*, 2003. 13(5):223-4, 227, 244.

170. Boucher FD, Modlin JF, Weller S, et al. Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. *J Pediatr*, 1993. 122(1):137-44.

171. Mirochnick M, Capparelli E, Dankner W, et al. Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. *Pediatr Res*, 1998. 42(4):808-12.

172. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr*, 2003. 142(1):47-52.

173. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*, 1998. 178(5):1327-33.

174. Moodley D, Pillay K, Naidoo K, et al. Pharmacokinetics of zidovudine and lamivudine in neonates following coadministration of oral doses every 12 hours. *J Clin Pharmacol*, 2001. 41(7):732-41.

175. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus--infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis*, 1999. 180(5):1536-41.

176. Rongkavilit C, Thaithumyanon P, Chuenyam T, et al. Pharmacokinetics of stavudine and didanosine coadministered with nelfinavir in human immunodeficiency virus-exposed neonates. *Antimicrob Agents Chemother*, 2001. 45(12):3585-90.

177. Wade N, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of d4T in combination with 3TC in HIV-Infected pregnant women and their infants (PACTG 332). 10th Conference on Retroviruses and Opportunistic Infections. Boston, MA, February 10-14, 2003 (Abstract 886).

178. Johnson GM, Rodman JH, McDowell M, et al. Preliminary analysis of abacavir succinate (ABC) pharmacokinetics in neonates differs from adults and young children. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, 2000. (Abstract 720).

179. Mirochnick M, Fenton T, Gagnier P, et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *J Infect Dis*, 1998. 178(2):368-74.

180. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis*, 1996. 174(4):713-21.

181. Mirochnick M, Siminski S, Fenton T, et al. Nevirapine pharmacokinetics in pregnant women and in their infants after in utero exposure. *Pediatr Infect Dis*, 2001. 20(8):803-5.
182. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after in utero exposure. *Pediatr Infect Dis J*, 2002. 21(9):835-8.
183. Litalien C, Faye A, Compagnucci A, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis*, 2003. 22(1):48-55.
184. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr*, 2002. 29(5):455-63.
185. Bryson Y, Stek A, Mirochnick M, et al. PACTG 353: a phase I study of safety, pharmacokinetics and antiviral activity of combination nelfinavir, ZDV and 3TC in HIV-infected pregnant women and their infants. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, 2000. (Abstract 715).
186. Sufka SA, Ferrari G, Gryszowka VE, et al. Prolonged CD4+ cell/virus load discordance during treatment with protease inhibitor-based highly active antiretroviral therapy: immune response and viral control. *J Infect Dis*, 2003. 187(7):1027-37.
187. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis*, 2001. 183(9):1328-35.
188. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. *J Infect Dis*, 2000. 181(3):946-53.
189. de Martino M, Galli L, Moriondo M, et al. Dissociation of responses to highly active antiretroviral therapy: Notwithstanding virologic failure and virus drug resistance, both CD4+ and CD8+ T lymphocytes recover in HIV-1 perinatally infected children. *J Acquir Immune Defic Syndr*, 2001. 26(2):196-7.
190. Eshleman SH, Krogstad P, Jackson JB, et al. Analysis of human immunodeficiency virus type 1 drug resistance in children receiving nucleoside analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir (Pediatric AIDS Clinical Trials Group 377). *J Infect Dis*, 2001. 183(12):1732-8.
191. Nijhuis M, Deeks S, Boucher C. Implications of antiretroviral resistance on viral fitness. *Curr Opin Infect Dis*, 2001. 14(1):23-8.
192. Devereux HL, Emery VC, Johnson MA, Loveday C. Replicative fitness in vivo of HIV-1 variants with multiple drug resistance-associated mutations. *J Med Virol*, 2001. 65(2):218-24.
193. Miller V, Haubrich R, Kuritzkes DR. Understanding Treatment-Resistant HIV, PRN Notebook. 2003. Available online at **http://www.prn.org**.
194. Durant J, Glevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet*, 1999. 353(9171):2195-9.
195. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS*, 2000. 14(9):F83-93.
196. Colgrove RC, Pitt J, Chung PH, et al. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS*, 1998. 12(17):2281-8.
197. Centers for Disease Control and Prevention. USPHS/IDSA Guidelines for the Prevention of opportunistic infections in persons infected with Human Immunodeficiency Virus. *MMWR*, 1997. 46(RR-12):1-46.
198. Piscitelli S, Vogel S, Sadler BM, et al. Effect of Efavirenz (DMP 266) on the pharmacokinetics of 141W94 in HIV-infected patients. In: Abstracts of the 5th Conference of Retroviruses and Opportunistic Infections. Chicago, IL, 1998. (Abstract 346):144.
199. Hilman RW. Tocopherol excess in man: Creatinuria associated with prolonged ingestion. *Am J Clin Nutr*, 1957. 5(6):597-600.
200. Johnson L, Bowen FW, Abbasi S, et al. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1,500 grams or less. *Pediatrics*, 1985. 75(4):619-38.
201. Lemons JA, Maisels MJ. Vitamin E: How much is too much? *Pediatrics*, 1985. 76(4):625-7.
202. Drug Information for the Health Care Professional (USP DI Vol. I). 19th Edition. Rockville, MD. The United States Pharmacopeial Convention, Inc. 1999. p. 2973-5.
203. Stuart MJ, Oski FA. Vitamin E and platelet function. *Am J Pediatr Hematol Oncol*, 1979. 1(1):77-82.
204. American Academy of Pediatrics, Committee on Drugs. "Inactive" ingredients in pharmaceutical products: update (subject review). *Pediatrics*, 1997. 99(2):268-78.