Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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 exposure to zidovudine (*ZDV*) and other antiretroviral medications in many perinatally infected children; c) differences in diagnostic evaluation in perinatal infection; d) differences in immunologic markers (e.g., CD4 $^{+}$ T-lymphocyte count) in young children; 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 treatment for 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 HIV/AIDS Treatment Information Service Website (http://www.hivatis.org).*

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 National Pediatric and Family HIV Resource Center (NPHRC). 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-lymphocyte count thresholds) and/or who had HIV-associated symptoms. Zidovudine (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 (e.g., 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

* 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.

of drug-resistant viral variants when antiretroviral treatment does not maximally suppress replication (2,3). New 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. A new class of antiretroviral drugs, protease inhibitors, has become available; these agents have reduced HIV viral load to levels that are undetectable and have reduced disease progression and mortality in many HIV-infected persons. 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).

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 developed by the U.S. Department of Health and Human Services Panel of Clinical Practices for Treatment of HIV Infection (5).

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 (e.g., 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, either 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 and to provide guidelines for antiretroviral treatment similar to those for HIV-infected adults (5), NPHRC, the Health Resources and Services Administration, 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.

The treatment recommendations provided in this report are based on published and unpublished data regarding the treatment of HIV infection in adults and children and, when no definitive data were available, the clinical experience of the Working Group members. The Working Group intended the guidelines to be flexible and not to supplant the clinical judgement of experienced

health-care providers. These guidelines will be modified by the Working Group as new information and clinical experience becomes available. The most recent information is available on the HIV/AIDS Treatment Information Service website (http://www.hivatis.org).

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 (8-10).
- 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 clinical trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children.
- All antiretroviral drugs approved for treatment of HIV infection may be used for children when indicated -- 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, social workers, psychologists, nutritionists, outreach workers, and pharmacists.
- Determination of HIV RNA copy number and $CD4^+$ T-lymphocyte 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 made available.

* In areas where enrollment in clinical trials is possible, enrolling the child in available trials should be discussed with the caregivers of the child. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDS Clinical Trials Information Service, telephone (800) 874-2572 ([800] TRIALS-A).

- Health-care providers considering antiretroviral regimens for 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 potential for the development of antiretroviral resistance.
- 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 during pregnancy. Universal HIV counseling and voluntary HIV testing with consent 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 and is endorsed by the Working Group (8-10).

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 (11); d) initiation of prophylaxis against *Pneumocystis carinii* pneumonia (PCP) in all HIV-exposed infants beginning at age 4-6 weeks in accordance with PHS guidelines (12); 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. For newborns in whom maternal serostatus was not determined during the prenatal or immediate postpartum period, HIV antibody should be tested for following counseling and consent of the mother. 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 4-6 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 in most infected infants by age 1 month and in virtually all infected infants by age 6 months by using viral diagnostic assays. A positive virologic test (i.e., detection of HIV by culture or DNA or RNA polymerase chain reaction [PCR]) 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. Testing at age 14 days also may be advantageous for early detection of infection. HIV-exposed infants should be evaluated by or in consultation with a specialist in HIV infection in pediatric patients.

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 PCR tests by age 48 hours (13). 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.

Assays that detect HIV RNA in plasma also may be useful for diagnosis of perinatal infection and may prove to be more sensitive than DNA PCR for early diagnosis of HIV infection in HIV-exposed infants (14). However, data are more limited regarding the sensitivity and specificity of HIV RNA assays compared with HIV DNA PCR for early diagnosis.

HIV culture has a sensitivity similar to that of DNA PCR for the diagnosis of infection (15). 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 use of 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 the sensitivity 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 <1 month because of a high frequency of false-positive assays during this time (16).

Initial testing is recommended by age 48 hours because nearly 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 negative virologic tests during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection (17). 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 (18,19). However, recent data from prospective cohort studies have demonstrated that although early differences in HIV RNA levels have been present between infants with 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 (20). 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 (20). 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 modification of antiretroviral therapy from the standard 6-week course of neonatal ZDV chemoprophylaxis to more aggressive combination antiretroviral therapy.

Infants with initially negative virologic tests should be retested at age 1-2 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 (4,21). However, 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.

HIV-exposed children who have had repeatedly negative virologic assays at birth and at age 1-2 months should be retested again at age 3-6 months. HIV infection is diagnosed by two positive HIV virologic tests performed on separate blood samples. HIV infection can be reasonably excluded among children with two or more negative virologic tests, two of which are performed at age $\geq$1 month, and one of those being performed at age $\geq$ 4 months (12). 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 among children with no clinical evidence of HIV infection. HIV infection can be definitively excluded if HIV IgG antibody is negative in the absence of hypogammaglobulinemia at age 18 months and if the child has both no clinical symptoms of HIV infection and negative HIV virologic assays.

Monitoring of Pediatric HIV Infection

Immunologic Parameters in Children

Clinicians interpreting $CD4^+$ T-lymphocyte number for children must consider age as a variable. $CD4^+$ T-lymphocyte 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 (22,23). 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) (24). Although the $CD4^+$ absolute number that identifies a specific level of immune suppression changes with age, the $CD4^+$ 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 $CD4^+$ cell count declines as HIV infection progresses, and patients with lower $CD4^+$ cell counts have a poorer prognosis than patients with higher counts (Table 3).

Because knowledge of immune status (i.e., $CD4^+$ T-lymphocyte count and percentage) is essential when caring for HIV-infected infants and children, $CD4^+$ T-lymphocyte values should be obtained as soon as possible after a child has a positive virologic test for HIV and every 3 months thereafter (25,26). Infected infants who have a thymic defect lymphocyte immunophenotypic profile (i.e., $CD4^+$ count <1,900/mm^3 and $CD8^+$ count >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 (27).

The $CD4^+$ T-lymphocyte count or percentage value is used in conjunction with other measurements to guide antiretroviral treatment decisions and primary prophylaxis for PCP after age 1 year. However, measurement of $CD4^+$ cell values can be associated with considerable intrapatient variation. Even mild intercurrent illness or the receipt of vaccinations can produce a transient decrease in $CD4^+$ cell number and percentage; thus, $CD4^+$ values are best measured when patients are clinically stable. No modification in therapy should be made in response to a change in $CD4^+$ 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 6-12 months following acute infection, reflecting the balance between ongoing viral production and immune elimination (28,29). 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 (30,31). 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 (32,33). 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 (20). 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 (20,34-36). 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.

Recent 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 have overlapped considerably (20,33). 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-lymphocyte percentage is

<15% (Table 4 and Table 5) (35). 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 (Table 6) (36). In this study, the relative risk for disease progression was reduced by 54% for each 1 $\log_{10}$ decrease in baseline HIV RNA level. Disease progression was documented in 11% of children aged <30 months at the time the study was initiated (mean age: 1.1 years) who had baseline RNA in the lowest quartile (e.g., from undetectable to 150,000 copies/mL) and in 52% of children with baseline RNA in the highest quartile (e.g., >1,700,000 copies/mL) (36). Among children aged ≥30 months at the time the study was initiated (mean age: 7.3 years), none of those with baseline RNA in the lowest quartile (e.g., undetectable to 15,000 copies/ mL) compared with 34% of those in the highest quartile (e.g., >150,000 copies/mL) had disease progression; children with RNA levels in the middle two quartiles (i.e., 15,000-50,000 and 50,001-150,000 copies/mL) had similar progression rates (13% and 16%, respectively). Data from children aged ≥30 months are similar to data from studies among infected adults, in which the risk for disease progression substantially increases when HIV RNA levels exceed 10,000-20,000 copies/mL (5).

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 (35). 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 (32). Additional data indicate that $CD4^+$ T-lymphocyte percentage and 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 (35,36). Similar data and conclusions recently have been reported from several studies involving infected adults (37-39).

Methodologic Considerations in the Interpretation and Comparability of HIV RNA Assays

Most of the published data regarding HIV RNA in children have been obtained using frozen, stored plasma and serum specimens. Some degradation of HIV RNA occurs with specimen storage and delay in specimen processing; thus, the published data on HIV RNA levels in infected children may not be directly comparable with data obtained from specimens that undergo immediate testing (e.g., specimens obtained for patient care). The HIV RNA assays used also differ by study. Therefore, direct extrapolation of the predictive value of HIV RNA levels reported in published studies to HIV RNA assays performed for clinical-care purposes may be problematic. Information from ongoing prospective studies will assist in the interpretation of HIV RNA levels among infected infants and children.

The use of HIV RNA assays for clinical purposes requires specific considerations (40), 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 $\log_{10}$) or more. For example, plasma RNA measured by the quantitative PCR assay (Amplicor HIV-1 Monitor™, manufactured by Roche Diagnostics Systems, Nutley, New Jersey) yields absolute values approximately twice (0.3 $\log_{10}$) those obtained using a signal amplification, branched-chain DNA assay (Quantiplex®, manufactured by Chiron Corporation, Emeryville, California) (5,41,42). Similarly, plasma RNA

measured by the nucleic acid sequence-based amplification assay (NASBA®, manufactured by Organon Technika, Durham, North Carolina) yields absolute values approximately twice those obtained using the Quantiplex® assay but values relatively comparable with those obtained using the Amplicor HIV-1 Monitor™ assay (41-43). Therefore, one HIV RNA assay method should be used consistently for monitoring each patient. Choice of HIV RNA assay, particularly for young children, may be influenced by the amount of blood required for the assay. The NASBA® 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 Quantiplex® 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 (5,39,44). 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 (20,34,35). This decline is most rapid during the first 12-24 months after birth, with an average decline of approximately 0.6 $\log_{10}$ per year; a slower decline continues until approximately age 4-5 years (average decline of 0.3 $\log_{10}$ per year). This inherent biologic variability must be considered when interpreting changes in RNA copy number in children. Thus, only changes 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

Adult guidelines for antiretroviral therapy are appropriate for post-pubertal 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 ideal 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 (45). Because many adolescents with HIV infection are sexually active, issues associated with contraception and prevention of HIV transmission should be discussed between the health-care provider and the adolescent.

Dosage for medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty (46) and not on the basis of age (25). 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. Youth

who are in their growth spurt (i.e., in females, Tanner Stage III and in males, Tanner Stage IV) should be closely monitored for medication efficacy and toxicity when using adult or pediatric dosing guidelines.

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 (47). Clinical experience with protease inhibitors and non-nucleoside reverse transcriptase inhibitor antiretroviral drugs is more limited.

Specific Issues of Adherence for HIV-Infected Children and Adolescents

Lack of adherence to prescribed regimens and subtherapeutic levels of antiretroviral medications may enhance the development of drug resistance. Data indicate that the development of resistance to one of the available protease inhibitor antiretrovirals may reduce susceptibility to some or all of the other available protease inhibitor drugs, thus substantially reducing subsequent treatment options. Similarly, the development of resistance to one of the available non-nucleoside reverse transcriptase inhibitors may be associated with resistance to the other members of the non-nucleoside reverse transcriptase inhibitor class of drugs. Therefore, education of infected children and/or their caregivers regarding the importance of compliance with the prescribed drug regimen is necessary when therapy is initiated and should be reinforced during subsequent visits. Many strategies can be used to increase medication adherence, including intensive patient education over several visits before therapy is initiated, the use of cues and reminders for administering drugs, development of patient-focused treatment plans to accommodate specific patient needs, and mobilization of social and community support services.

Adherence to drug regimens is especially problematic for children. 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. 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. 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.

A comprehensive assessment of adherence issues should be instituted for all children in whom antiretroviral treatment is considered; evaluations should include nursing, social, and behavioral assessments. 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 facing families that may affect adherence to complex medical regimens. For some families, certain issues (e.g., 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.

HIV-infected adolescents have specific adherence problems. 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. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include a) denial and fear of their HIV infection; b) misinformation; c) distrust of the medical establishment; d) fear and lack of belief in the effectiveness of medications; e) low self-esteem; f) unstructured and chaotic lifestyles; and g) 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 adults. 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.

TREATMENT RECOMMENDATIONS

Initiation of Antiretroviral Therapy

General Considerations

Antiretroviral therapy has provided substantial clinical benefit to HIV-infected children with immunologic or clinical symptoms of HIV infection. Studies have demonstrated substantial improvements in neurodevelopment, growth, and immunologic and/or virologic status with initiation of ZDV, didanosine (ddI), lamivudine (3TC), or stavudine monotherapy (48-53). More recent pediatric trials of symptomatic children who have not previously received antiretrovirals 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 (36,54,55). A trial involving children who have previously received antiretrovirals has demonstrated that combination therapy that includes a protease inhibitor is virologically and immunologically superior to dual nucleoside combination therapy (56).

Data from clinical trials that address the effectiveness of antiretroviral therapy in asymptomatic infants and children with normal immune function are not available. However, initiation of therapy early in the course of HIV infection, including during the period of primary infection in the neonate, is theoretically advantageous. Control of viral replication in perinatally infected

infants is inadequate, as demonstrated by the high levels of HIV RNA that are observed during the first 1-2 years of life following perinatal infection. Initiation of aggressive antiretroviral therapy during this early period of viral replication could theoretically preserve immune function, diminish viral dissemination, lower the viral set point, and result in improved clinical outcome.

In a preliminary study of early treatment of children, six HIV-infected infants aged 2-4 months were placed on a regimen of ZDV, ddI, and nevirapine; baseline HIV RNA levels were 40,000-1,500,000 copies per mL. Five of six infants had an early virologic response with a drop in RNA PCR to <10,000 copies/mL by day 14, and two of the infants maintained undetectable levels of HIV RNA through 168 days of therapy (57). These two children had persistently negative HIV cultures, undetectable RNA levels, and became HIV antibody negative, although HIV DNA PCR remained positive. Clinical trials are ongoing to assess the virologic, immunologic, and clinical response of young infants to early, aggressive antiretroviral therapy with three or four antiretroviral agents.

The theoretical problems with early therapy include the potential for short- and long-term adverse effects -- particularly for drugs being administered to infants aged <6 months, for whom information on pharmacokinetics, drug dosing, and safety is limited. These concerns are particularly relevant because life-long administration of therapy is likely to be necessary for HIV-infected infants. If viral replication is not suppressed, ongoing viral mutation is likely to result in the development of antiretroviral resistance, curtailing the duration of benefit that early therapy might confer and potentially limiting future treatment options. Therefore, intensive education of care-givers and patients about the importance of adherence to the prescribed treatment regimen should be provided before therapy is initiated so that a) potential problems and solutions can be identified and b) frequent follow-up can be provided to assess virologic response to therapy, drug tolerance, and adherence.

When to Initiate Therapy

Antiretroviral therapy is recommended for HIV-infected children with clinical symptoms of HIV infection (i.e., those in clinical categories A, B, or C) (Table 2) or evidence of immune suppression (i.e., those in immune categories 2 or 3) (Table 1) -- regardless of the age of the child or viral load (Table 7). Clinical trial data from both adults and children have demonstrated that antiretroviral therapy in symptomatic patients slows clinical and immunologic disease progression and reduces mortality (54,55,58).

Ideally, antiretroviral therapy should be initiated in all HIV-infected infants aged <12 months as soon as a confirmed diagnosis is established -- regardless of clinical or immunologic status or viral load. HIV-infected infants aged <12 months are considered at high risk for disease progression, and the predictive value of immunologic and virologic parameters to identify infants who will have rapid progression is less than that for older children. Identification of infection during the first few weeks 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, clinical trial data documenting therapeutic benefit from this approach are not available, and information on drug dosing in neonates is limited. Because resistance to antiretroviral drugs (particularly protease inhibitors) can develop rapidly when drug concentrations fall below therapeutic levels (either as a result of inadequate dosage or

incomplete adherence), issues associated with adherence should be fully assessed and discussed with the HIV-infected infant's caregivers before the decision to initiate therapy is made.

Two general approaches for initiating therapy in asymptomatic children aged ≥1 year were outlined by the Working Group. The first approach would be to initiate therapy in all HIV-infected children, regardless of age or symptom status. Such an approach would ensure a) treatment of infected children as early as possible in the course of disease and b) intervention before immunologic deterioration. Data from prospective cohort studies indicate that most HIV-infected infants will have clinical symptoms of infection by age 1 year (59,60). Most asymptomatic infected children aged >1 year also have $CD4^+$ T-lymphocyte percentages of <25% (60), which is indicative of immunosuppression (Table 1) and warrants antiretroviral therapy.

An alternative approach would be to 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., low viral load) and when other factors (e.g., concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, the health-care provider should regularly monitor virologic, immunologic, and clinical status. Factors to be considered in deciding when to initiate therapy include a) high or increasing HIV RNA levels, b) rapidly declining $CD4^+$ T-lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (i.e., immune category 2 [Table 1]), or c) development of clinical symptoms. The level of HIV RNA considered indicative of increased risk for disease progression is not well defined for young children. Regardless of age, any child with HIV RNA levels of >100,000 copies/mL is at high risk for mortality (Table 4), and antiretroviral therapy should be initiated -- regardless of clinical or immune status. HIV RNA levels in asymptomatic children aged ≥30 months that are the same as levels for which there are treatment recommendations for HIV-infected adults (e.g., >10,000-20,000 copies/mL) also may indicate the need to initiate treatment (Table 6). In addition, any child with HIV RNA levels that demonstrate a substantial increase (more than a 0.7 $\log_{10}$ [fivefold] increase for children aged <2 years and more than a 0.5 $\log_{10}$ [threefold] increase for those aged ≥2 years) on repeated testing should be offered therapy -- regardless of clinical or immunologic status or absolute level of viral load. These recommendations are based on limited data and may need revision as more information becomes available.

Issues associated with adherence to treatment are especially important in considering whether and when to initiate therapy. Antiretroviral therapy is most effective in patients who have never received therapy 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. 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.

Choice of Initial Antiretroviral Therapy

Combination therapy is recommended for all infants, children, and adolescents who are treated with antiretroviral agents (Table 8). When compared with monotherapy, combination therapy a) slows disease progression and improves survival, b) results in a greater and more sustained virologic response, and c) delays development of virus mutations resistant to the drugs being used. Monotherapy with the currently available antiretroviral drugs is no longer recommended to

treat HIV infection. ZDV monotherapy is appropriate, however, when used in infants of indeterminate HIV status during the first 6 weeks of life to prevent perinatal HIV transmission. Infants who are identified as being HIV-infected while receiving ZDV chemoprophylaxis should be changed to a combination antiretroviral drug regimen.

Aggressive antiretroviral therapy for primary perinatal infection with three drugs is recommended 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. Based on clinical trials involving infected adults, the preferred regimen is combination therapy with two NRTIs and one protease inhibitor. Although these combinations have had limited evaluation in clinical trials involving children, they can reduce HIV RNA to undetectable levels in some children (61,62). An interim analysis from a clinical trial of children (i.e., PACTG protocol 338) has demonstrated that therapy with drug combinations that include a protease inhibitor is more effective than therapy with two NRTI antiretroviral drugs in reducing viral load to undetectable levels and increasing $CD4^+$ T-lymphocyte number (56). Recent data, primarily from adults, with the use of efavirenz (Sustiva) in place of the protease inhibitor may support the substitution of efavirenz for the protease inhibitor. The only available data regarding safety, dosing and virologic and immunologic efficacy of efavirenz in children are from an open-label study of efavirenz combined with nelfinavir and NRTIs in 57 pediatric patients (PACTG 382), some as young as age 3 years. In a preliminary intent-to-treat analysis, after 20 weeks of therapy, 65% of children had plasma HIV RNA levels <400, and 52% had HIV RNA levels <50 copies/mL (71,72). However, there are currently no pharmacokinetic data available on appropriate dosage of efavirenz in children under age 3 years, and although a liquid preparation is currently under study, only a capsular formulation is currently available. New antiretroviral drugs and combinations are being studied in infected adults and children. Other drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles most likely will become available, which 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 potential limitations in subsequent treatment options should resistance develop.

Protease inhibitors with formulations appropriate for infants and children who cannot swallow pills include nelfinavir (Viracept®, manufactured by Agouron Pharmaceuticals, Inc., La Jolla, California), available in a powder formulation that can be mixed with water or food, ritonavir (Norvir®, manufactured by Abbott Laboratories, North Chicago, Illinois), and amprenavir (Agenerase™, manufactured by Glaxo Wellcome, Inc., Research Triangle Park, NC), both available in a liquid formulation. Optimal dosing of these drugs in children aged <2 years is not known but is being evaluated in clinical trials (See Appendix). Indinavir (Crixivan®, manufactured by Merck and Company, Inc., West Point, Pennsylvania) and saquinavir (hard gel capsule, Invirase™, and soft gel capsule, Fortovase™, manufactured by Hoffman-LaRoche, Inc., Nutley, New Jersey) are not available in liquid formulations. Indinavir is recommended for consideration for children who can tolerate swallowing capsules. Optimal dosing of these drugs in infants and children is not known but is being evaluated in clinical trials (See Appendix). The hard-gel capsule formulation of saquinavir (Invirase™) has limited bioavailability and thus is not recommended for use with two NRTIs. Some studies have indicated substantial increases in saquinavir drug levels when coadministered with other protease inhibitors (e.g., ritonavir) or other drugs that inhibit the cytochrome P450 enzyme system. However, data regarding such

combinations in children are not available. The soft-gel formulation of saquinavir (Fortovase™) with enhanced bioavailability has been approved by the Food and Drug Administration (FDA) for treatment of HIV infection in adults; however, data regarding appropriate dosing of this formulation in pediatric patients are not available.

Amprenavir in combination with 2 NRTIs is a regimen which may be offered in special circumstances in selected pediatric patients as initial antiretroviral therapy and also may have utility in antiretroviral-experienced patients. The combination of zidovudine, lamivudine and amprenavir resulted in an HIV RNA of <400 copies/ml in 53% of treatment naïve adults after 24 weeks of therapy (80). In an ongoing open label, randomized phase III trial of 504 NRTI and NNTRI experienced but PI naïve adults comparing amprenavir and indinavir in combination with 2 NRTIs (PROAB3006), 43% and 53% of patients respectively had HIV RNA < 400 copies/ml after 24 weeks of therapy using an intent-to-treat analysis (83) . In a study of 41 treatment naïve adults, the combination of amprenavir and abacavir resulted in a fall in HIV RNA levels to <5 copies/ml in 58% of patients after 60 weeks of therapy (79). In HIV-infected pediatric patients, the combination of amprenavir with 2 NRTIs resulted in a decrease in HIV RNA to <400 copies/ml in 41% of antiretroviral- experienced patients treated for 8 weeks (82).

The FDA approved formulation of amprenavir contains 46 IU of vitamin E/ml of oral solution and 109 IU vitamin E per 150 mg capsule. The recommended dose of amprenavir 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 amprenavir 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 for adults is 30 IU per day. The liquid formulation also contains propylene glycol in a concentration that exceeds WHO standards for use in infants. Young infants have immature levels of alcohol dehydrogenase enzymes which are involved in the metabolism of propylene glycol. The serum half-life of propylene glycol in neonates is prolonged at 16.9 hours compared with a half-life of 5 hours in adults. There is concern that the propylene glycol contained in the liquid formulation may not be metabolized adequately and could cause toxicity. High levels of propylene glycol have been associated with hyperosmolality, lactic acidosis, seizures and respiratory depression (87).

Because of the lack of long term data on the use of amprenavir and the lack of data on its use in treatment naïve children, it should be recommended as initial therapy only in special circumstances. This agent should not be used in children < 3 years of age because of the lack of data in children < 3 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.

Amprenavir may be included as a component of a treatment regimen for children who have failed prior protease inhibitor therapy. Therapy with amprenavir induces mutations in HIV-1 protease gene at codons 46, 47, 50, 54 and 84. At least 2-3 mutations are required at codons 46, 47 and 50 to produce >10 fold decrease in sensitivity. None of the other PIs induced a mutation at codon 50 in vitro.

Alternative regimens, although not ideal, may be considered for initial therapy in circumstances in which the caregiver has concerns regarding the feasibility of adherence to a complex drug regimen or when the patient and caregivers prefer an alternative regimen. Alternative regimens have been clinically beneficial in adult and pediatric patients, but these regimens may not suppress viral load to below detectable levels as consistently as does combination therapy with

two NRTIs and a protease inhibitor. An example of such alternative regimens include combination regimens of two NRTIs with nevirapine substituted for the protease inhibitor or two NRTIs alone. However, drug regimens that do not result in sustained viral suppression may result in the development of viral resistance to the drugs being used.

The combination of abacavir, ZDV, and 3TC resulted in a viral load of <400 copies/mL in 74% of treatment-naive adults at 48 weeks of therapy, results similar to those of a protease inhibitor-containing regimen. (73,74). However, in a study of infected infants who had received only prior ZDV preventive therapy, this combination produced suppression of viral replication to <400 copies/mL in only 4 of 11 subjects by 12 weeks of treatment. (Catherine Wilfert, M.D., personal communication) This 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. (75, 76, 77) However, because the uncertain long-term durability of viral load suppression with a regimen comprised of three drugs of a single class (NRTIs), because results in the infected infant are disappointing, and because abacavir is associated with a potentially life-threatening hypersensitivity syndrome, a protease inhibitor-containing or efavirenz-containing regimen is preferred. Insufficient clinical trial data are available to guide the optimal use of abacavir in combination with protease inhibitors and/or non-nucleoside reverse transcriptase inhibitors.

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 (63), 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 (64). Data do not suggest that the antiretroviral regimen for infected infants should be chosen on the basis of maternal antiretroviral use. However, continuing to monitor the frequency of perinatal transmission of antiretroviral-resistant HIV isolates is crucial, because maternal therapy with multiple antiretroviral agents is becoming more common and the prevalence of resistant viral strains in the HIV-infected population may increase over time.

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 (65). 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 (See Appendix).

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 (e.g., those born before 34 weeks' gestation) (66). Appropriate ZDV dosing for premature infants has not been defined but is being evaluated in a phase I clinical trial of premature infants born before 34 weeks' gestation (i.e., PACTG protocol 331) (See Appendix).

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 (67,68).

Clearance was prolonged in these infants. On the basis of data from this study, the dose recommended for use in newborns is half the dose recommended in older children (See Appendix). No data are available regarding 3TC pharmacokinetics among infants aged 2-6 weeks, and the exact age at which 3TC clearance begins to approximate that in older children is not known.

Nevirapine administration to HIV-infected pregnant women during labor and as a single dose to their newborns at age 2-3 days has been studied in a phase I trial (69). The half-life of nevirapine was prolonged in neonates compared with that in older children, indicating that some modification of nevirapine dosage is required for administration to neonates (See Appendix).

Although phase I studies of several protease inhibitors (i.e., indinavir, ritonavir, nelfinavir, or saquinavir in combination with ZDV and 3TC) in pregnant infected women and their infants are ongoing in the United States, no data are available regarding drug dosage, safety, and tolerance of any of the protease inhibitors in neonates.

Changing Antiretroviral Therapy

When to Change Antiretroviral Therapy

The following three reasons warrant a change in antiretroviral therapy: a) failure of the current regimen with evidence of disease progression based on virologic, immunologic, or clinical parameters; b) toxicity or intolerance to the current regimen; and c) new data demonstrating that a drug or regimen is superior to the current regimen (Table 9). When therapy must be changed because of treatment failure or suboptimal response to treatment, clinicians should work with families to assess the possible contribution of adherence problems to the failure of the current regimen. Issues regarding adherence should be addressed to increase the likelihood of a successful outcome when initiating a new therapy. These issues are best addressed before therapy is instituted and need to be reinforced during therapy.

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 needed to support and educate the family and to monitor adherence, tolerance, and virologic response to the new regimen.

Virologic Considerations for Changing Therapy

Information is limited regarding HIV RNA response to antiretroviral therapy in infants and young children. However, 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 below levels capable of being detected with HIV RNA assays -- which 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). The recommendations for adults state that health-care providers should consider changing therapy if a) HIV RNA levels drop less than threefold (0.5 $\log_{10}$) after 4 weeks of therapy and less than 10-fold (1.0 $\log_{10}$) after 8 weeks of therapy or b) HIV RNA has not decreased to undetectable levels after 4-6 months of therapy. 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 (i.e., 8-12 weeks). 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 two NRTIs and a protease inhibitor. 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 initially assessed 4 weeks after therapy is initiated. 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. If baseline HIV RNA levels are high (i.e., >1,000,000 copies/mL), virologic response may not be observed until 8-12 weeks after initiating antiretroviral therapy. However, if baseline HIV RNA levels are more similar to those observed in untreated infected adults (i.e., <100,000 copies/mL), initial response should be observed within 4 weeks following initiation of 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. The following situations may indicate a need for change in therapy in infected children:

- Less than a minimally acceptable virologic response after 8-12 weeks of therapy. For children receiving antiretroviral therapy with two NRTIs and a protease inhibitor, such a response is defined as a <10-fold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (i.e., dual NRTI combinations), an insufficient response is defined as a less than fivefold (0.7 $\log_{10}$) decrease in HIV RNA levels from baseline.
- HIV RNA not suppressed to undetectable levels after 4-6 months of antiretroviral therapy. However, although suppression of HIV RNA to undetectable levels and maintenance for prolonged periods is desirable, few data among children indicate that such suppression is 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 had undetectable levels in response to antiretroviral therapy. The presence of repeatedly detectable RNA suggests the development of resistance or problems with adherence or drug bioavailability. More frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (e.g., if using an HIV RNA assay with a lower limit of detection of 1,000 copies/mL, there is a $\leq$0.7 $\log_{10}$ increase from undetectable to approximately 5,000 copies/mL in an infant aged <2 years). If adherence to therapy has been inconsistent, renewed efforts to educate the caregivers and patient and closer follow-up from members of a multidisciplinary care team may improve adherence.
- 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 initiation of the therapeutic regimen, 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-lymphocyte count and percentage are independent predictors of disease progression and mortality in HIV-infected children (35,36). The association of HIV RNA and $CD4^+$ percentage with long-term mortality risk in HIV-infected children has been evaluated; for each absolute decline of five percentiles in $CD4^+$ 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 (35). For children with $CD4^+$ percentages of <15% (i.e., those in immune category 3), prognosis also was correlated with the degree of depression of $CD4^+$ percentage (i.e., life expectancy was less for children with $CD4^+$ percentages of <5% compared with children with $CD4^+$ percentages of 10%-14%) (Table 3).

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

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

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., persistence or progression of deterioration documented on repeated testing as demonstrated by the presence of two or more of the following findings: 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 (e.g., ZDV or nevirapine, 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 (Table 2)). Prognosis is poorer as patients progress to more advanced clinical categories (59). However, in patients with stable immunologic and virologic parameters, progression from one clinical category to another (e.g., 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 and the limited 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. New regimens should be chosen partly on the basis of 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. However, antiretroviral drugs should only be reduced to the lower end of the therapeutic range for those antiretrovirals for which an effective dosing range is known, and adequacy of antiretroviral activity should be confirmed by the monitoring of HIV RNA levels.

- When changing therapy because of treatment failure (Table 9), adherence to therapy should be assessed as a potential cause of failure.
- If the patient is adherent to the prescribed drug regimen, assume the development of drug resistance and, if possible, change at least two drugs to new antiretroviral agents. Change in one drug or addition of a drug to a failing regimen is suboptimal. The new regimen should include at least three drugs, if possible. The potential for cross-resistance between antiretroviral drugs should be considered in choosing new drugs.
- When considering changing to a new regimen, all other medications taken by the patient should be reviewed for possible drug interactions.
- A change to a new regimen, especially one containing protease inhibitors, must include a discussion of treatment adherence issues between the caregivers of the infected child and the health-care provider. 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.
- When changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered.

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

It is important to distinguish between the need to change therapy due to drug failure versus drug toxicity or poor compliance. Viral resistance to antiretroviral drugs is important, but not the only reason for treatment failure. The goal of antiretroviral therapy should be to reduce plasma HIV RNA to below detection of the most sensitive assay available (<50 copies/mL). Accomplishing optimal viral suppression will reduce the likelihood that genetic/phenotypic resistance will emerge.

Genotypic 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 1000 copies/mL of HIV RNA. Expert clinical interpretation is required to determine if genomic variations coincide with changes known to be associated with antiretroviral resistance. A compilation of the most common HIV-1 mutations selected by the three classes of antiretroviral agents is available on the Internet at http://hiv-web.lanl.gov.

Phenotypic assays measure the 50% or 90% inhibitory concentrations of a drug against the virus in vitro. These assays historically have been cumbersome and time-consuming. However, more rapid assays based on recombinant DNA technology are being developed. Although phenotypic assays provide important information regarding the sensitivity patterns of the dominant virus tested, minor species of resistant viruses may be missed.

HIV resistance assays may prove useful in guiding initial therapy and in changing failing regimens. However, the value of phenotypic or genotypic assays in guiding treatment has not

been established in children. Moreover, standardization of such assays will be necessary before guidelines can be established for the incorporation of these assays into clinical care. Epidemiological surveys are needed to monitor the prevalence of resistant viruses in specific pediatric populations.

Therefore, specific recommendations cannot be made at this time regarding use of resistance assays for directing antiretroviral drug choices in children. However, if resistance testing is performed to determine its contribution to drug failure, these assays should be done while the child is still receiving antiretroviral drugs. In the absence of antiretroviral drug pressure, wild type virus is likely to replace resistant strains that could mask the presence of resistant virus.

It should be noted that the presence of viral resistance to a particular drug suggests that the specific drug(s) is unlikely to be successful in suppressing viral replication. However, the absence of resistance to a drug does not insure that its use will be successful, particularly if that drug or drugs share cross-resistance with drugs previously used. Although initial studies performed in adults suggest that drug-resistance genotyping modestly improves the response to antiretroviral therapy as reflected by a decline in HIV RNA levels below 200 copies/ml (78), there are no long-term data on the impact of such testing. Moreover, no controlled clinical trials, to date, have been performed in children that assess the benefits of genotypic or phenotypic resistance.

MANAGING ADVERSE DRUG REACTIONS IN THE THERAPY OF PEDIATRIC HIV INFECTION

The antiretroviral agents used and approved to treat HIV infection in children have all demonstrated individual and drug-class toxicities that limit the doses and combinations that can be used safely (70). The general principles of toxicity management are similar for adults and children. However, for many of the newer therapies (particularly the protease inhibitors), limited short-term and no long-term safety data or experience are available for infants, children, and adolescents. Thus, the amount of information on which to base guidelines for management of antiretroviral toxicities in children, especially when antiretroviral drugs are used in combination, is substantially more limited than that for adults. The data available from PACTG protocol 152 and PACTG protocol 300 indicate that some combinations of nucleoside analogues do not substantially increase the toxicity relative to monotherapy with those agents (54,55).

The toxicities of antiretroviral drugs may occur at different frequencies in children and adults, and the implications of some of the toxicities substantially differ for children. The most obvious difference for children from the listing of toxicities in the adult guidelines is the increased indirect bilirubin associated with indinavir, which is labeled as inconsequential for adults. This toxicity could be of major consequence for newborn and young infants because severe hyperbilirubinemia is associated with kernicterus and would require specific monitoring and treatment should indinavir be administered to neonates. Additional examples of differences of potential toxicities between adults and children include the description of asymptomatic retinal depigmentation in children associated with ddI therapy and the relative lack of pancreatitis in children compared with adults receiving ddI therapy (See Appendix).

Another treatment issue that affects children differently from adults concerns the feasibility of administering poorly palatable liquid antiretroviral formulations to children. Innovative

techniques to increase palatability may be needed to enable tolerance of medications (e.g., various methods can be used to increase tolerance of ritonavir [See Appendix]). Indinavir is associated with hematuria and nephrolithiasis secondary to crystallization of the drug in the urine; adequate hydration (i.e., 48 oz of fluid daily) is recommended to reduce the incidence of this side effect. However, ensuring that voluntary fluid intake of this level is achieved may be more difficult in children than in adults.

All efforts should be made to continue therapy in the presence of toxicities that are not life threatening. Such efforts should include liberal use of adjunctive measures (e.g., granulocyte colony stimulating factor for treatment of neutropenia and erythropoietin and/or transfusions for treatment of anemia). If antiretroviral therapy must be discontinued for an extended period of time, to minimize the risk for developing drug resistance, all antiretroviral agents should be stopped simultaneously rather than continuing one or two agents alone because of potential increased viral replication.

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-lymphocyte and percentage*

	< 12 mos		1- 5 yrs		6-12 yrs	
Immune category	**No./mL**	**(%)**	**No./mL**	**(%)**	**No./mL**	**(%)**
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): 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 **two** or more of the following conditions but none of the conditions listed in categories B and C:

- Lymphadenopathy ($\geq$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/mm^3), or thrombocytopenia (<100,000/mm^3) persisting $\geq$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).

* 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): 1-10.

TABLE 3. Association of baseline CD4$^+$ T-lymphocyte percentage with long-term risk for death in human immunodeficiency virus (HIV)-infected children [*]

		Deaths [†]	
Baseline	**No. Patients[§]**	**No.**	**(%)**
< 5%	33	32	(97%)
5% - 9%	29	22	(76%)
10% - 14%	30	13	(43%)
15% - 19%	41	18	(44%)
20% - 24%	52	13	(25%)
25% -29%	49	15	(31%)
30% - 34%	48	5	(10%)
≥ 35%	92	30	(33%)

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

[†] Mean follow-up: 5.1 years

[§] Includes 374 patients for whom baseline CD4$^+$ T-lymphocyte percentage data were available.

Source: Mofenson L, 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;175:1029-38

TABLE 4. Association of baseline human immunodeficiency virus (HIV) RNA copy number with long-term risk for death in HIV-infected children [*]

Baseline (copies/mL)[§]	No. patients [¶]	Deaths [†]	
		No.	(%)
Undetectable (i.e., ≤4,000)	25	6	(24%)
4,001 – 50,000	69	19	(28%)
50,001 – 100,000	33	5	(15%)
100,001 – 500,000	72	29	(40%)
500,001 – 1,000,000	20	8	(40%)
> 1,000,000	35	25	(71%)
Total	**254**	**92**	**(36%)**

[*] 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 Corporation, Durham, North Carolina) on frozen stored serum.

[¶] Mean age: 3.4 years.

Source: Mofenson L, 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;175:1029-38.

TABLE 5. Association of baseline human immunodeficiency virus (HIV) RNA copy number and CD4+ T-lymphocyte percentage with long-term risk for death in HIV-infected children*

Baseline HIV RNA§ (copies/mL) / Baseline CD4+ T-lymphocyte 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 Corporation, Durham, North Carolina) on frozen stored serum.

¶ Mean age: 3.4 years.

Source: Mofenson L, 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;175:1029-38.

TABLE 6. Association of baseline human immunodeficiency virus (HIV) RNA quartile by age at entry with risk for disease progression or death during study follow - up among HIV- infected children receiving antiretroviral treatment[*]

Age at entry/Baseline HIV RNA quartiles (copies/mL) [†]	No. patients	Disease progression or death	
		No.	(%)
< 30 months [§]			
<1,000 – 150,000	79	9	(11%)
150,001 – 500,000	66	13	(20%)
500,001 – 1,700,000	76	29	(38%)
> 1,700,000	81	42	(52%)
≥ 30 months [¶]			
<1,000 – 15,000	66	0	(0%)
15,001 – 50,000	54	7	(13%)
50,001 – 150,000	80	13	(16%)
> 150,000	64	22	(34%)

[*] Data from the Pediatric AIDS Clinical Trial Group protocol 152.

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

[§] Mean age: 1.1 years.

[¶] Mean age: 7.3 years.

Source: Palumbo PE, Raskino C, Fiscus S, et al. Disease progression in HIV-infected infants and children: predictive value of quantitative plasma HIV RNA and CD4 lymphocyte count. *JAMA* 1998; 279:756-61.

TABLE 7. Indications for initiation of antiretroviral therapy in children with human immunodeficiency virus (HIV) infection *

- Clinical symptoms associated with HIV infection (i.e., clinical categories A, B, or C [Table 2]).
- Evidence of immune suppression, indicated by $CD4^+$ T- lymphocyte absolute number or percentage (i.e., immune category 2 or 3 [Table 1]).
- Age < 12 months – regardless of clinical, immunologic, or virologic status.
- For asymptomatic children aged $\geq$ 1 year with normal immune status, two options can be considered:

  1. Preferred Approach

     Initiate therapy – regardless of age or symptom status.

  2. Alternative Approach

     Defer treatment in situations in which the risk for clinical disease progression is low and other factors (e.g., concern for the durability of response, safety, and adherence) favor postponing treatment. In such cases, the health-care provider should regularly monitor virologic, immunologic, and clinical status. Factors to be considered in deciding to initiate therapy include the following:

     - High or increasing HIV RNA copy number.
     - Rapidly declining $CD4^+$ T-lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (i.e., immune category 2 [Table 1]).
     - Development of clinical symptoms.

* Indications for initiation of antiretroviral therapy in post-pubertal HIV-infected adolescents should follow the adult guidelines (Office of Public Health and Science, Department of Health and Human Services. Availability of report of NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV-infected adults. Federal Register 1997; 62:33417-8.)

TABLE 8. Recommended antiretroviral regimens for initial therapy for human immunodeficiency virus (HIV) infection in children

Strongly Recommended

Clinical trial evidence of clinical benefit and/or sustained suppression of HIV replication in adults and/or children.

- One highly active protease inhibitor plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs)
  - Preferred protease inhibitor for infants and children who cannot swallow pills or capsules: *nelfinavir or ritonavir*. Alternative for children who can swallow pills or capsules: *indinavir*.
  - Recommended dual NRTI combinations: the most data on use in children are available for the combinations of *zidovudine (ZDV*) and *dideoxyinosine (ddI)* and for *ZDV* and *lamivudine (3TC)*. More limited data are available for the combinations of *stavudine (d4T)* and *ddI*, *d4T* and *3TC*, and *ZDV* and *Zalcitabine (ddC)*. *
- Alternative for children who can swallow capsules: Efavirenz (Sustiva)** plus 2 NRTIs (see above) or efavirenz (Sustiva) plus nelfinavir and 1 NRTI.

Recommended as an Alternative

Clinical trial evidence of suppression of HIV replication, but 1) durability may be less in adults and/or children than with strongly recommended regimens; or 2) the durability of suppression is not yet defined; or 3) evidence of efficacy may not outweigh potential adverse consequences (e.g., toxicity, drug interactions, cost, etc).

- *Nevirapine* and two NRTIs.
- *Abacavir* in combination with ZDV and 3TC.

Offer only in Special Circumstances

Clinical trial evidence of 1) limited benefit for patients; or 2) data are inconclusive, but may be reasonably offered in special circumstances.

- Two NRTIs
- Amprenavir in combination with 2 NRTIs or abacavir

Not Recommended

Evidence against use because of 1) overlapping toxicity; and/or 2) because use may be virologically undesirable.

- Any monotherapy ¶
- d4T and ZDV
- ddC and ddI
- ddC and d4T
- ddC and 3TC

* ddC is not available in a liquid preparation commercially, although a liquid formulation is available through a compassionate use program of the manufacturer (Hoffman-LaRoche Inc., Nutley, New Jersey). ZDV and ddC is a less preferred choice for use in combination with a protease inhibitor.

** Efavirenz is currently available only in capsule form, but liquid preparation is currently being evaluated. There are currently no data on appropriate dosage of efavirenz in children under age 3 years.

¶ Except for ZDV chemoprophylaxis administered to HIV-exposed infants during the first 6 weeks of life to prevent perinatal HIV transmission; if an infant is identified as HIV-infected while receiving ZDV prophylaxis, therapy should be changed to a combination antiretroviral drug regimen.

TABLE 9. 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 antiretroviral therapy with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a protease inhibitor, such a response is defined as a < 10-fold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (i.e., dual NRTI combinations), an insufficient response is defined as a less than five fold (0.7 $\log_{10}$) decrease in HIV RNA levels from baseline.
- HIV RNA not suppressed to undetectable levels after 4-6 months of antiretroviral therapy. †
- Repeated detection of HIV RNA in children who initially responded to antiretroviral therapy with undetectable levels. §
- 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 initiation of the therapeutic regimen, 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-lymphocyte percentages of < 15% (i.e., those in immune category 3), a persistent decline of five percentiles or more in $CD4^+$ cell percentage (e.g., from 15% to 10%).
- A rapid and substantial decrease in absolute $CD4^+$ T-lymphocyte count (e.g., a >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.
- Disease progression defined as advancement from one pediatric clinical category to another (e.g., from clinical category A to clinical category B) **.

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

† The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5 to 2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels.

§ More frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (e.g., if when using an HIV RNA assay with a lower limit of detection of 1,000 copies/mL, there is a $\leq$0.7 $\log_{10}$ increase from undetectable to approximately 5,000 copies/mL in an infant aged < 2 years).

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

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Appendix

CHARACTERISTICS OF AVAILABLE ANTIRETROVIRAL DRUGS

Nucleoside Analogue Reverse Transcriptase Inhibitors [*] [†]

Abacavir (GW 1592U89)(ABC) Ziagen™

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

Dosage:

Neonatal dose: Not approved for infants less than 3 months of age. In infants between 1 and 3 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.

Major toxicities

Most frequent: Nausea, vomiting, headache, fever, rash, anorexia, and fatigue.

Unusual (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. 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 6 weeks of therapy. Patients suspected of having a hypersensitivity reaction should have ABC stopped and not restarted since hypotension and death have occurred upon rechallange.

Uncommon: Diarrhea, pancreatitis, increased liver enzymes, elevated blood glucose, elevated triglycerides, lactic acidosis.

Drug Interactions

- No significant interactions between ABC, zidovudine (ZDV), and lamivudine (3TC).

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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.

Drug Interaction - (Cont.)

- Abacavir 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 abacavir, 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).

Didanosine (dideoxyinosine) (ddI), VIDEX◊

Preparations: Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL; Chewable tablets with buffers: 25, 50, 100, and 150 mg; Buffered powder for oral solution: 100, 167, and 250 mg.

Dosage

Neonatal 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: 90 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.)

Adolescents/Adult dose: Body weight $\geq$60 kg: 200 mg twice daily. Body weight <60 kg: 125 mg twice daily.

Major toxicities

Most frequent: Diarrhea, abdominal pain, nausea, and vomiting.

Usual (more severe): Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia.

Uncommon: 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 2 hours before or 2 hours after ddI.
- Tetracycline and fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets); administer 2 hours before or 2 hours after ddI.

Drug interactions (Cont.)

- Concominant administration of ddI and delavirdine may decrease the absorption of these drugs; separate dosing by at least 2 hours.
- Administration with protease inhibitors: indinavir should be administered at least 1 hour before or after ddI on an empty stomach. Ritonavir should be administered at least 2 hours before or after ddI.

Special instructions

- ddI formulation contains buffering agents or antacids.
- Food decreases absorption; administer ddI on an empty stomach (1 hour before or 2 hours after a meal). Further evaluation in children regarding administration with meals is under study.
- 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 (e.g., if the child's dose is 50 mg, administer two 25-mg tablets and not one 50-mg tablet).

Lamivudine (3TC), EPIVIR®

Preparations: Solution: 10 mg/mL; Tablets: 150 mg

Dosage

Neonatal 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 $\geq$50 kg: 150 mg twice daily. Body weight <50 kg: 2 mg per kg of body weight twice daily.

Major toxicities

Most frequent: Headache, fatigue, nausea, diarrhea, skin rash, and abdominal pain.

Unusual (more severe): Pancreatitis (primarily seen in children with advanced HIV infection receiving multiple other medications), peripheral neuropathy, decreased neutrophil count, and increased liver enzymes.

Drug interactions

- Trimethoprim/sulfamethoxazole (TMP/SMX) increases 3TC blood levels (possibly competes for renal tubular secretion); unknown significance.
- When used with zidovudine (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®

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

Dosage

Neonatal 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.

Major toxicities

Most frequent: Headache, gastrointestinal disturbances, and skin rashes.

Uncommon (more severe): Peripheral neuropathy and pancreatitis.

Other: Increased liver enzymes.

Drug interactions

- Drugs that decrease renal function could decrease clearance.
- Should not be administered in combination with zidovudine (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.

Zalcitabine (ddC), HIVID®

Preparations: Syrup: 0.1 mg/mL (investigational); Tablets: 0.375 and 0.75 mg.

Dosage

Neonatal dose: Unknown

Pediatric usual dose: 0.01 mg per kg of body weight every 8 hours.

Pediatric dosage range: 0.005 to 0.01 mg per kg of body weight every 8 hours.

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

Major toxicities

Most frequent: Headache, gastrointestinal disturbances, and malaise.

Unusual (more severe): Peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, and skin rashes.

Drug interactions

- Cimetidine, amphotericin, foscarnet, and aminoglycosides may decrease renal clearance of ddC.
- Antacids decrease absorption 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

- Administer on an empty stomach (1 hour before or 2 hours after a meal).
- Decrease dosage in patients with impaired renal function.

Zidovudine (ZDV, AZT), RETROVIR®

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

Dosage

Dose for premature infants: (Standard neonatal dose may be excessive in premature infants.) Under study in Pediatric AIDS Clinical Trial Group protocol 331: 1.5 mg per kg of body weight every 12 hours from birth to 2 weeks of age; then increase to 2 mg per kg of body weight every 8 hours after 2 weeks of age.

Neonatal dose: Oral: 2 mg per kg of body weight every 6 hours. Intravenous: 1.5 mg per kg of body weight every 6 hours.

Pediatric usual dose: Oral: 160 mg per m^2 of body surface area every 8 hours. Intravenous (intermittent infusion): 120 mg per m^2 of body surface area every 6 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 6-8 hours.

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

Major toxicities

Most frequent: Hematologic toxicity, including granulocytopenia and anemia, and headache.

Unusual: Myopathy, myositis, and liver toxicity.

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.

Drug interactions (Cont.)

- The following drugs may increase ZDV concentration (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 4 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 1 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 1 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 [*] [†]

Delavirdine (DLV), RESCRIPTOR®

Preparations: Tablets: 100 mg

Dosage

Neonatal dose: Unknown.

Pediatric dose: Unknown.

Adolescent/Adult dose: 400 mg three times a day.

Major toxicities

Most frequent: 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 (e.g., astemizole or terfenadine); sedative-hypnotics (e.g., alprazolam, midazolam, or triazolam); calcium channel blockers (e.g., 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 (e.g., phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.
- Absorption of DLV is decreased if given with antacids or histamine$_2$ receptor antagonists.

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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 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.

Drug interactions (Cont.)

- 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 saquinavir and indinavir, resulting in a significant increase in saquinavir and indinavir concentrations and a slight decrease in DLV concentrations.

Special instructions

- Can be administered with food.
- Should be taken 1 hour before or 1 hour after ddI or antacids.
- Tablets can be dissolved in water and the resulting dispersion taken promptly.

Efavirenz (DMP-266), Sustiva™

Preparations: Capsules: 50, 100 and 200 mg.

Dosage

Neonatal 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 currently no data available on the appropriate dosage for children under age 3 years.

Adult/adolescent dose: 600 mg once daily

Major toxicities

Most frequent: 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 (astemizole or terfenadine), sedative-hypnotics (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).

Drug interactions (Cont.)

- Enzyme inducers such as rifampin, rifabutin, phenobarbital and phenytoin may decrease efavirenz concentrations; clinical significance unknown.
- Efavirenz is highly plasma protein bound, and has the potential for drug interactions with other highly protein bound drugs (eg., 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 efavirenz.
- Administration with protease inhibitors: Coadministration decreases levels of saquinavir (area under the curve [AUC] decreased by 50%) and indinavir (AUC decreased by 31%). Coadministration of saquinavir as a sole protease inhibitor is not recommended; indinavir dose should be increased if given with efavirenz (for adults, from 800 mg to 1000 mg every 8 hours). Coadministration increases levels of both ritonavir and efavirenz (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 nelfinavir (AUC increased by 20%) but no dose adjustment is needed.

Special instructions

- Efavirenz can be taken with and without food. The relative bioavailability of efavirenz 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 efavirenz 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 efavirenz has a peppery taste; grape jelly has been used to disguise the taste.
- Bedtime dosing is recommended, particularly during the first 2-4 weeks of therapy, to improve tolerability of central nervous system side effects.

Nevirapine (NVP), VIRAMUNE®

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

Dosage

Neonatal dose (through age 3 months): Under study in Pediatrics AIDS Clinical Trial Group protocol 365: 5 mg per kg of body weight once daily for 14 days, followed by 120 mg per m^2 of body surface area every 12 hours for 14 days, followed by 200 mg per m^2 of body surface area every 12 hours.

Pediatric dose: 120 to 200 mg per m^2 of body surface area every 12 hours. Note: Initiate therapy with 120 mg per m^2 of body surface area administered once daily for 14 days. Increase to full dose administered every 12 hours if there are no rash or other untoward effects.

Adolescent/Adult dose: 200 mg every 12 hours. Note: Initiate therapy at half dose for the first 14 days. Increase to full dose if there is no rash or other untoward effects.

Major toxicities

Most frequent: Skin rash (some severe and life-threatening, including Stevens-Johnson syndrome), sedative effect, headache, diarrhea, and nausea.

Unusual: Elevated liver enzymes and, rarely, hepatitis.

Drug interactions

- Induces hepatic cytochrome P450 3A (CYP3A); autoinduction of metabolism occurs in 2-4 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.
- Drugs having suspected interactions which should be used only with careful monitoring: rifampin and rifabutin; oral contraceptives (alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control); sedative-hypnotics (e.g., triazolam or midazolam); oral anticoagulants; digoxin; phenytoin; or theophylline.
- Administration with protease inhibitors: indinavir and saquinavir concentrations are decreased significantly, and ritonavir concentrations may be decreased. Whether increased doses of protease inhibitors are needed is unknown.

Special instructions

- Can be administered with food.
- May be administered concurrently with ddI.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. 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).
- For investigational suspension: Must be shaken well; store at room temperature.

* 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.

Protease Inhibitors [*] [†] [§]

Amprenavir (APV)(Agenerase)

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

Dosage

Neonatal Dose: No pharmacokinetic data on dosing in children less than age 3 years.

Pediatric/Adolescent Dose (<50kg): Oral Solution: 22.5 mg/kg bid or 17mg/kg tid (maximum daily dose 2,800 mg). Capsules: 20 mg/kg bid or 15 mg/kg tid (maximum daily dose 2,400 mg)

Adults Dose: 1,200 mg (eight 150 mg capsules) bid

Major toxicities

Most frequent: Vomiting, nausea, diarrhea, perioral parethesias, and rash.

Unusual (more severe): Life-threatening rash, including Stevens-Johnson syndrome in 1% of patients.

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

Drug interactions

- Amprenavir 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 efavirenz and amprenavir lowers levels of amprenavir 39%. (81)
- Amprenavir should not be administered concurrently with astemizole, bepridil, cisapride, dihydorergotamine, 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 amprenavir.

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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 (Cont.)

- Rifampin has been found to reduce plasma concentrations of amprenavir (decreased AUC 82%) and should not be used with amprenavir. Amprenavir has no significant effect on rifampin plasma levels.
- The AUC of rifabutin is increased by 193% when given in combination with amprenavir. The dose of rifabutin should be reduced by at least half the recommended dose when given in combination with amprenavir.
- Coadministration of amprenavir 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 hypotention, visual changes, and priapism.
- The FDA approved formulation of amprenavir contains 46 IU of vitamin E/ml of oral solution and 109 IU vitamin E per 150 mg capsule. The recommended dose of amprenavir 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 amprenavir 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 30 IU per day for adults. 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 amprenavir should be advised not to take supplemental vitamin E (84, 85, 86, 88, 89).
- The liquid formulation of amprenavir 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 5 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 (87).
- The efficacy of hormonal contraceptives may be reduced in patients receiving amprenavir. Alternate or additional methods of birth control should be co-administered if coadministering with hormonal methods of birth control.
- Other medications that are substrates, inhibitors or inducers of CYP3A4 could also potentially interact with amprenavir. See Product Information for Agenerase for complete list of other drugs, which may potentially interact with amprenavir.
- Amprenavir is a sulfonamide. The potential for cross sensitivity between drugs in the sulfonamide class and amprenavir is unknown. Amprenavir should be used with caution in patients with sulfonamide allergy.

Special Instructions

- Amprenavir should not be used in children less than 3 years of age because of the lack of data in children < 3 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.
- Amprenavir may be taken with or without food, but should not be given with a high fat meal (6.7 Milky Way bars) as there is a 21% decrease in the AUC when amprenavir is administered after a high fat meal of 67 grams of fat compared with the fasting state.
- Patients taking antacids (or ddI) should take amprenavir at least 1 hour before or after antacid (or ddI) use.

Indinavir, CRIXIVAN®

Preparations; Capsules: 200 and 400 mg.

Dosage

Neonatal 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 8 hours.

Adolescents/Adults: 800 mg every 8 hours.

Major toxicities

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

Unusual (more severe): Nephrolithiasis (4%) and exacerbation of chronic liver disease.

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. ¶

¶ 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.

Drug interactions (Cont.)

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Indinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Indinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; or sedative-hypnotics (e.g., triazolam or midazolam).
- Indinavir 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 indinavir concentrations (consider reducing adolescent/adult indinavir dose to 600 mg every 8 hours).
- Coadministration of clarithromycin increases serum concentration of both drugs (dosing modification not needed).
- Coadministration of nevirapine may decrease indinavir serum concentration.
- Administration with other protease inhibitors: coadministration with nelfinavir increases concentration of both drugs; coadministration with saquinavir increases concentration of saquinavir.

Special Instructions

- Administer on an empty stomach 1 hour before or 2 hours after a meal (or can take with a light meal).
- Adequate hydration required to minimize risk of nephrolithiasis (at least 48 oz of fluid daily in adult patients).
- If co-administered with ddI, give at least 1 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.

Nelfinavir, VIRACEPT®

Preparations: Powder for oral suspension: 50 mg per 1 level gram scoop full (200 mg per 1 level teaspoon); Tablets: 250 mg tablet

Dosage

Neonatal dose: Under study in Pediatric AIDS Clinical Trial Group protocol 353: 40 mg per kg of body weight two times a day. (Note: no preliminary data available, investigational.)

Pediatric dose: 20 to 30 mg per kg of body weight three times a day; many experts would administer a *minimum* dose of 30 mg per kg body weight three times a day.

Adolescent/Adult dose: 750 mg three times a day.

Major toxicities

Most frequent: Diarrhea.

Less common: Asthenia, abdominal pain, rash, and exacerbation of chronic liver disease.

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

Drug interactions

- Nelfinavir 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.
- Nelfinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Nelfinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (e.g., quinidine or amiodarone); or sedative-hypnotics (e.g., triazolam or midazolam).
- Nelfinavir levels are greatly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin causes less decline in nelfinavir concentrations; if coadministered with nelfinavir, rifabutin should be reduced to one half the usual dose.
- Estradiol levels are reduced by nelfinavir, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- Coadministration with delavirdine (DLV) increases nelfinavir concentrations twofold and decreases DLV concentrations by 50%. There are no data on co-administration with nevirapine, but some experts use higher doses of nelfinavir if used in combination with nevirapine.
- Administration with other protease inhibitors: coadministration with indinavir increases concentration of both drugs; coadministration with saquinavir increases concentration of saquinavir with little change in nelfinavir concentration; coadministration with ritonavir increases concentration of nelfinavir without change in ritonavir concentration.

Special instructions

- Administer with meal or light snack.
- If coadministered with ddI, nelfinavir should be administered 2 hours before or 1 hour after ddI.
- For oral solution: powder may be mixed with water, milk, pudding, ice cream, or formula (for up to 6 hours).
- Do not mix with any acidic food or juice because of resulting poor taste.

Special instructions (cont.)

- 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.

Ritonavir, NORVIR®

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

Dosage

Neonatal dose: Under study in Pediatric AIDS Clinical Trial 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 5 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 5 days as tolerated.

Major toxicities

Most frequent: Nausea, vomiting, diarrhea, headache, abdominal pain, and anorexia.

Less common: Circumoral paresthesias and increase in liver enzymes.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

Drug interactions

- 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.
- Not recommended for concurrent use with analgesics (e.g., meperidine, piroxicam, or propoxyphene); antihistamines (e.g., astemizole or terfenadine); certain cardiac drugs (e.g., amiodarone, bepridil hydrochloride, encainide hydrochloride, flecainide acetate, propafenone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (e.g., alprazolam, clorazepate, diazepam, estazolam, flurazepam hydrochloride,

* 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.

Drug interactions (Cont.)

midazolam, triazolam, or zolpidem tartrate); certain psychotropic drugs (e.g., bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin.

- Estradiol levels are reduced by ritonavir, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- Ritonavir increases metabolism of theophylline (levels should be monitored, and dose may need to be increased).
- Ritonavir 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).
- Ritonavir 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 ritonavir include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because ritonavir can affect the metabolism of these drugs as well).
- Administration with other protease inhibitors: co-administration with saquinavir and nelfinavir increases concentration of these drugs with little change in ritonavir concentration.

Special instructions

- Administration with food increases absorption.
- If ritonavir is prescribed with ddI, there should be 2 hours between taking each of the drugs.
- Oral solution must be kept refrigerated and stored in original container; can be kept at room temperature if used within 30 days.
- To minimize nausea, therapy should be initiated at a low dose and increased to full dose over 5 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, INVIRASE™ (hard gel capsule) and FORTOVASE™ (soft gel capsule)

Preparations: Hard gel capsules: 200 mg; Soft gel capsules: 200 mg

Dosage

Neonatal dose: *Unknown.*

Pediatric dose: *Unknown (will be studied in Pediatric AIDS Clinical Trials Group protocol 397).*

Adolescent/Adult dose: Hard gel capsules: 600 mg three times a day; Soft gel capsules: 1200 mg three times a day.

Major toxicities

Most frequent: Diarrhea, abdominal discomfort, headache, nausea, paresthesias, and skin rash.

Less common: Exacerbation of chronic liver disease.

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

Drug interactions

- Saquinavir 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.
- Saquinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Saquinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives, or sedative-hypnotics (e.g., midazolam or triazolam).
- Saquinavir levels are significantly reduced with concurrent use of rifampin (decreases saquinavir levels by 80%), rifabutin (decreases saquinavir levels by 40%), and nevirapine (decreases saquinavir levels by 25%).
- Saquinavir levels are decreased by carbamazepine, dexamethasone, phenobarbital, and phenytoin.
- Saquinavir levels are increased by delavirdine and ketoconazole.
- Saquinavir may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be closely monitored for toxicity.
- Administration with other protease inhibitors: coadministration with indinavir, ritonavir, or nelfinavir increases concentration of saquinavir with little change in concentration of the other drug.

* 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.

Special instructions

- Administer within 2 hours of a full meal to increase absorption.
- Concurrent administration of grapefruit juice increases saquinavir concentration.
- Sun exposure can cause photosensitivity reactions, therefore sunscreen or protective clothing is recommended.