

# Antiretroviral Therapy and Medical Management of Pediatric HIV Infection

ABBREVIATIONS. NPHRC, National Pediatric and Family HIV Resource Center; ZDV, zidovudine; PI, protease inhibitor; PACTG, Pediatric AIDS Clinical Trials Group; NIH, National Institutes of Health; DHHS, Department of Health and Human Services; HRSA, Health and Human Resources Administration; USPHS, US Public Health Service; IDSA, Infectious Diseases Society of America; FDA, Food and Drug Administration; OI, opportunistic infection; PCP, *Pneumocystis carinii* pneumonia; PCR, polymerase chain reaction; CI, confidence interval; NRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; 3TC, lamivudine; ddI, didanosine; d4T, stavudine; ddC, zalcitabine; IDV, indinavir; SQV, saquinavir; RTV, ritonavir; NFV, nelfinavir; CNS, central nervous system; CSF, cerebrospinal fluid; NVP, nevirapine; DLV, delavirdine; MAC, *Mycobacterium avium* complex; VZV, varicella-zoster virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; BAL, bronchoalveolar lavage; G-CSF, granulocyte colony stimulating factor; IVIG, intravenous immunoglobulin; LIP, lymphoid interstitial pneumonia; TMP/SMX, trimethoprim/sulfamethoxazole; TB, tuberculosis; MMR, measles-mumps-rubella; STD, sexually transmitted disease; HPV, human papilloma virus; RDA, Recommended Daily Allowance; DEXA, dual x-ray absorptiometry; TPN, total parenteral nutrition; PE, progressive encephalopathy; ADC, AIDS dementia complex; SE, static encephalopathy; CT, computed tomography; MRI, magnetic resonance imaging; EPS, extrapyramidal syndrome; ADHD, attention deficit/hyperactivity disorder; PNS, peripheral nervous system; NMDA, N-methyl-D-aspartate; EMLA, eutectic mixture of local anesthetics.

These guidelines were developed by the Working Group on Antiretroviral Therapy and Medical Management of Infants, Children and Adolescents with HIV Infection convened by the National Pediatric and Family HIV Resource Center (NPHRC), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). The Co-Chairs of the Working Group were James Oleske, MD, MPH, University of Medicine and Dentistry of New Jersey (UMDNJ)-New Jersey Medical School, Newark, NJ and Gwendolyn B. Scott, MD, University of Miami School of Medicine, Miami, FL.

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## INTRODUCTION

In 1993, the Working Group on Antiretroviral Therapy and Medical Management of HIV-infected Children, composed of specialists in the care of infants, children, and adolescents with HIV infection, 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

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(based on age-related CD4<sup>+</sup> 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 (eg, isolated lymphadenopathy or hepatomegaly) and normal immune status was not recommended.<sup>1</sup>

Since the Working Group developed these recommendations, dramatic advances have been made in laboratory and clinical research. The rapidity and magnitude of HIV replication during all stages of infection are greater than believed previously and account for the emergence of drug-resistant viral variants when antiretroviral treatment does not maximally suppress replication.<sup>2,3</sup> 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 drug, protease inhibitor (PI) agents, has become available; these agents have reduced HIV viral load to levels that are undetectable with currently available assays and have reduced disease progression and mortality in many patients with HIV infection. 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 diminished substantially with the use of a regimen of ZDV administered during pregnancy and labor and to the newborn<sup>4</sup> (Appendix).

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 patients with HIV infection has been formulated by the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection (Table 1).<sup>5</sup> Treatment recommendations for infected adults and postpubertal adolescents have been developed by the Department of Health and Human Services (DHHS) Panel of Clinical Practices for Treatment of HIV Infection.<sup>6</sup>

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 patients, HIV-infected infants, children, and adolescents require unique considerations. Most HIV infection among children is 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 (ie, primary) HIV infection. 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 previous exposure to

**TABLE 1.** Principles of Therapy of HIV Infection

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4<sup>+</sup> T-cell destruction, whereas CD4<sup>+</sup> T-cell counts indicate the extent of HIV-induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4<sup>+</sup> T-cell counts is necessary to determine the risk of disease progression in an HIV-infected individual and to determine when to initiate or modify antiretroviral treatment regimens.
3. As rates of disease progression differ among individuals, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4<sup>+</sup> T-cell counts.
4. The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.
5. The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been treated previously and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
6. Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
7. The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy increases future therapeutic constraints.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. Persons with acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
10. HIV-infected persons, even those with viral loads below detectable limits, should be considered infectious and should be counseled to avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infectious pathogens.

The information in this table is derived from reference 5.

ZDV and other antiretroviral drugs used during pregnancy and the neonatal period for maternal treatment or to prevent perinatal transmission, or both.<sup>7,8</sup> 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,<sup>6</sup> NPHRC, the Health and Human Resources Administration (HRSA), and NIH reconvened the Working Group on Antiretroviral Therapy and Medical Management of HIV-infected Children, consisting of specialists in the care of HIV-infected children and adolescents, family members of HIV-infected children, and governmental 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. In addition to antiretroviral therapy, the Working Group addressed the following issues relative to pediatric HIV disease: 1) managing drug toxicity, and 2) managing the complications of HIV infection.

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 intends for the guidelines to be flexible and to not supplant the clinical judgment of experienced health care providers. The first portion of this supplement, sections on background and guidelines for initiating and changing antiretroviral therapy, do not differ substantively from their recent presentation in *MMWR*<sup>9</sup> except for some minor editorial changes and additions reflecting new developments since the earlier publication was prepared. The second and third portions of the supplement, not published previously, address the management of common toxicities associated with medications used frequently in treating HIV infections and the common complications of HIV infection. The final section, reprinted as a companion piece to these pediatric guidelines, is the recent US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) publication, *1997 Guidelines for the Prevention of Opportunistic Infections in Person Infected with Human Immunodeficiency Virus*, published recently in *MMWR*.<sup>10</sup> Clearly these guidelines will need to be modified frequently as new information and clinical experience accrue.

## BACKGROUND

### Concepts Considered in Formulating Pediatric Treatment Guidelines

Guidelines for the therapy of HIV disease, particularly with regard to antiretroviral therapy, continue to evolve as new data become available from clinical trials, new drugs are approved, and the pathogenesis of HIV disease is elucidated further. The availability of antiretroviral drugs for infected children has lagged behind that for infected adults. This is in part attributable to the smaller number of infected children available for participation in clinical trials compared with the number of infected adults, the belief that large efficacy studies in children are necessary to obtain a pediatric indication for a new drug, and difficulties in the development of drug formulations appropriate for pediatric use. The approval of drugs for use in children was facilitated by the 1994 Food and Drug Administration (FDA) ruling that a pediatric drug indication may be obtained by provision of data from controlled clinical trials in adults along with pharmacokinetic and safety data in pediatric patients if the disease course and effects of a drug are sufficiently similar in children and adults. Thus, many of the data on antiretroviral drugs have come from clinical trials in infected adults. However, pediatric treatment guidelines must take into account

the unique considerations related to HIV disease in infants, children, and adolescents. In consideration of limited pediatric data, the Working Group used the following general principles related to therapy of infectious diseases as a foundation for development of pediatric guidelines:

- The earliest possible diagnosis and treatment of an infection optimizes clinical outcome.
- The effectiveness of antimicrobial therapy is assessed by measuring changes in the quantity of the infectious agent in the patient.
- The goal of therapy for an infectious disease is to eradicate the infectious agent or, if eradication is not possible, to obtain a sustained decrease to the lowest possible level in replication of the organism.
- Combination antimicrobial therapy should be used if it is documented that drug resistance emerges when a single drug is given for therapy.
- When combination antimicrobial therapy is used, drugs with different sites/mechanisms of action and nonoverlapping toxicities should be used whenever possible.
- When eradication of the infectious agent is not possible, resulting in a chronic infection, therapy should be changed when the patient develops laboratory or clinical evidence of disease progression.
- In the setting of a fatal infection, aggressive measures and a greater tolerance for adverse drug events are acceptable risks when choosing treatment regimens.

In addition to the general infectious disease principles above, the Working Group identified a number of important concepts that need to be taken into consideration in the formulation of the current and future pediatric antiretroviral treatment guidelines. These concepts include the following:

- Identification of women with HIV infection 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.<sup>11-13</sup>
- Enrollment of pregnant women with HIV infection, their HIV-exposed newborns, and infected infants, children, and adolescents into clinical trials affords the best means of determining safe and effective therapies. In areas where enrollment into clinical trials is possible, enrollment of the child into available trials should be discussed with the caregivers of the child. Information about clinical trials for adults and children with HIV infection can be obtained by calling 1-800-TRIALS-A.
- 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, con-

current clinical trials are needed for children 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 in children when indicated—irrespective of labeling notations.<sup>a</sup>
- Management of HIV infection in infants, children, and adolescents is evolving rapidly 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 specialists 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 in adults and, therefore, assays to measure these variables should be made available.
- Health care providers considering antiretroviral regimens for children and adolescents should take into account certain factors influencing adherence to therapy, including 1) availability and palatability of pediatric formulations; 2) impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to co-administer with other prescribed medications, and need to take with or without food; 3) 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 4) 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 children with HIV infection. 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.

<sup>a</sup>Information included in these guidelines may not represent 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.

## Identification of Perinatal HIV Exposure

Appropriate treatment of infants with HIV infection requires HIV-exposed infants to be identified as soon as possible, which can be best accomplished through the identification of women with HIV infection before or during pregnancy. Universal HIV counseling and voluntary HIV testing with consent are recommended as standard of care for all pregnant women in the United States by the USPHS, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists and are endorsed by the Working Group.<sup>11-13</sup>

Early identification of women with HIV infection is crucial for the health of such women and for care of HIV-exposed and -infected children. Knowledge of maternal HIV infection during the antenatal period enables 1) HIV-infected women to receive appropriate antiretroviral therapy and prophylaxis against opportunistic infection (OI) for their own health; 2) provision of antiretroviral chemoprophylaxis with ZDV during pregnancy and labor, and to their newborn to reduce the risk for HIV transmission from mother to child<sup>4,7,8</sup>; 3) counseling of infected women about the risks for HIV transmission through breast milk and advising against breastfeeding in the United States and other countries where safe alternatives to breast milk are available<sup>14</sup>; 4) initiation of prophylaxis against *Pneumocystis carinii* pneumonia (PCP) in all HIV-exposed infants beginning at age 4 to 6 weeks in accordance with PHS guidelines<sup>15</sup>; and 5) early diagnostic evaluation of HIV-exposed infants to permit early initiation of aggressive antiretroviral therapy.

If women are not tested for HIV during pregnancy, counseling and HIV testing should be recommended during the immediate postnatal period. Newborns in whom maternal serostatus was not determined during the prenatal or immediate postpartum period should be tested for HIV antibody after 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 PCP prophylaxis should be initiated at age 4 to 6 weeks in all infants born to HIV-infected women. Those infants who have been abandoned, are in the custody of the state, or who have positive toxicology screening test results 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 diagnosed definitively in most infected infants by age 1 month and in virtually all infected infants by age 6 months using viral diagnostic assays. A positive virologic test result (ie, detection of HIV by culture, DNA, or RNA polymerase chain reaction [PCR]) indicates probable 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 48 hours of age, at 1 to 2 months, and at 3 to 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. Of infected children, 38% (90% confidence interval [CI] = 29%–46%) had positive PCR test results by 48 hours of age.<sup>16</sup> 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 PCR-positive 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.<sup>17</sup> 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 sensitivity similar to that of DNA PCR for the diagnosis of infection.<sup>18</sup> However, HIV culture is more complex and expensive to perform than is DNA PCR, and definitive results may not be available for 2 to 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 is less than that for the other HIV virologic tests. P24 antigen testing alone is not currently recommended to exclude infection or for diagnosis of infection for infants younger than 1 month because of a high frequency of false-positive assays during this time.<sup>19</sup>

Initial testing is recommended by age 48 hours because nearly 40% of infected infants can be identified at this time. Blood samples obtained 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 with positive virologic test results before age 48 hours are considered to have early (ie, intrauterine) infection, whereas infants with negative virologic test results during the first week of life and subsequent positive tests are considered to have late (ie, intrapartum) infection.<sup>20</sup> Some researchers have proposed that infants with early infection may have more rapid disease progression than those with late infection and therefore should be treated with a more aggressive therapeutic approach.<sup>21,22</sup> However, recent data from prospective cohort studies have demonstrated that although early differences in HIV RNA levels were present in infants with positive HIV culture within 48 hours of birth compared with those with first positive culture after age 7 days, these differences were no longer statistically significant after age 2 months.<sup>23</sup> HIV RNA copy number after the first month of life was more prognostic of rapid disease progression than the time when HIV culture test

results became positive. 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 test results should be retested at age 1 to 2 months. With increasing use of ZDV to reduce perinatal transmission, most HIV-exposed neonates will receive 6 weeks of antiretroviral chemoprophylaxis. Although prophylactic antiretroviral therapy theoretically could effect the predictive value of HIV virologic testing in neonates, ZDV monotherapy did not delay the detection of HIV by culture in infants in PACTG 076 and has not decreased the sensitivity and predictive values of many virologic assays.<sup>4,24</sup> 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 with repeated negative virologic assays at birth and at age 1 to 2 months should be retested again at age 3 to 6 months. HIV infection is diagnosed by two positive HIV virologic test results from separate blood samples. HIV infection can be reasonably excluded among children with two or more negative virologic test results, two performed at age  $\geq 1$  month and one performed at age  $\geq 4$  months.<sup>15</sup> Two or more negative HIV IgG antibody test results obtained at age  $> 6$  months with an interval of at least 1 month between tests also can be used to reasonably exclude HIV infection in children with no clinical evidence of HIV infection. HIV infection can be excluded definitively 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 Pediatric HIV Infection

### *Immunologic Parameters in Children*

Clinicians interpreting CD4+ T-lymphocyte number in 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.<sup>25,26</sup> A pediatric clinical and immunologic staging system for HIV infection has been developed that includes age-related definitions of immune suppression (Tables 2, 3).<sup>27</sup> 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 to identify disease progression in children. In infected children and adults, CD4+ cell count declines as HIV infection progresses, and patients with lower CD4+ cell counts

**TABLE 2.** 1994 Revised Pediatric HIV Classification System: Immunologic Categories Based on Age-specific CD4+ Lymphocyte Count and Percentage

Immune Category	Age of Child					
	<12 mo		1-5 y		6-12 y	
	Number/ $\mu$ L	(%)	Number/ $\mu$ L	(%)	Number/ $\mu$ L	(%)
Category 1: no suppression	$\geq 1500$	( $\geq 25$ )	$\geq 1000$	( $\geq 25$ )	$\geq 500$	( $\geq 25$ )
Category 2: moderate suppression	750-1499	(15-24)	500-999	(15-24)	200-499	(15-24)
Category 3: severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

Modified from Centers for Disease Control. 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.

have a poorer prognosis than do patients with higher counts (Table 4).

Because knowledge of immune status (ie, 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.<sup>28,29</sup> Infected infants who have a congenital thymic defect lymphocyte immunophenotypic profile (ie, CD4+ count <1900/mm<sup>3</sup> and CD8+ count >850/mm<sup>3</sup>) during the first 6 months of life have had more rapid HIV disease progression than do infants who do not have this profile.<sup>30</sup>

The CD4+ T-lymphocyte count or percentage value is used in conjunction with other measurements to guide antiretroviral treatment decisions and primary prophylaxis of PCP after age 1 year. However, measurement of CD4+ cell values can be associated with considerable inpatient variation. Even mild intercurrent illness or undergoing vaccination 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 at least 1 week between measurements.

#### HIV RNA in Children

Viral burden in peripheral blood can be determined 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 two to three log<sub>10</sub> copies to reach a stable lower level (ie, the virologic setpoint) ~ 6 to 12 months after acute infection, reflecting the balance between ongoing viral production and immune elimination.<sup>31,32</sup> Below is a guide to interpret log changes in HIV RNA copies. Several studies conducted in 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 setpoints.<sup>33,34</sup> 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.<sup>6</sup> These recommendations also are applicable to infected adolescents, particularly those who have acquired HIV infection via drug use and/or

sexual contact. These recommendations also are likely to be applicable to perinatally infected children older than 3 years.

#### A GUIDE TO LOGARITHMIC CHANGES IN HIV RNA COPY NUMBER

LOG <sub>10</sub> DECLINE	FOLD CHANGE	HIV RNA LEVELS (COPIES/ML) FOLLOWING DESIGNATED LOG <sub>10</sub> DECLINE FROM BASELINE LOAD OF 100,000 COPIES/ML
0.3	2 fold	50,000 copies
0.5	3 fold	33,000 copies
0.6	4 fold	25,000 copies
0.7	5 fold	20,000 copies
1.0	10 fold	10,000 copies
1.5	30 fold	3,300 copies
2.0	100 fold	1,000 copies
2.3	200 fold	500 copies

The HIV RNA pattern in perinatally infected infants differs from that in infected adults. High HIV RNA copy numbers persist among infected children for prolonged periods.<sup>35,36</sup> In one prospective study, HIV RNA levels were generally low at birth (ie, <10 000 copies/mL), increased to high values by age 2 months (most infants had values >100 000 copies/mL ranging from undetectable in rare infants 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.<sup>23</sup> 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.<sup>23,37-39</sup> This pattern likely 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 (ie, >299 000 copies/mL) in infants younger than 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.<sup>23,36</sup> High RNA levels (ie, levels >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% (Tables 5, 6).<sup>38</sup> Similar findings have been reported in a preliminary analysis of data from

**TABLE 3.** 1994 Revised HIV 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 conditions listed below but none of the conditions listed in categories B and C.
<ul style="list-style-type: none"> <li>▶ Lymphadenopathy (<math>\geq 0.5</math> cm at more than two sites; bilateral = one site)</li> <li>▶ Hepatomegaly</li> <li>▶ Splenomegaly</li> <li>▶ Dermatitis</li> <li>▶ Parotitis</li> <li>▶ Recurrent or persistent upper respiratory infection, sinusitis or otitis media</li> </ul>
Category B: Moderately Symptomatic
Children who have symptomatic conditions other than those listed for category A or C that are attributed to HIV infection. Examples of conditions in clinical category B include but are not limited to:
<ul style="list-style-type: none"> <li>▶ Anemia (<math>&lt; 8</math> gm/dL), neutropenia (<math>&lt; 1000/\text{mm}^3</math>) or thrombocytopenia (<math>&lt; 100\,000/\text{mm}^3</math>) persisting <math>\geq 30</math> d</li> <li>▶ Bacterial meningitis, pneumonia, or sepsis (single episode)</li> <li>▶ Candidiasis, oropharyngeal (thrush) persisting (<math>&gt; 2</math> months) in children <math>&gt; 6</math> m</li> <li>▶ Cardiomyopathy</li> <li>▶ Cytomegalovirus infection, with onset before 1 month of age</li> <li>▶ Diarrhea, recurrent or chronic</li> <li>▶ Hepatitis</li> <li>▶ HSV stomatitis, recurrent (more than two episodes within 1 year)</li> <li>▶ HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age</li> <li>▶ Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome</li> <li>▶ Leiomyosarcoma</li> <li>▶ LIP or pulmonary lymphoid hyperplasia complex</li> <li>▶ Nephropathy</li> <li>▶ Nocardiosis</li> <li>▶ Persistent fever (lasting <math>&gt; 1</math> month)</li> <li>▶ Toxoplasmosis, onset before 1 month of age</li> <li>▶ Varicella, disseminated (complicated chickenpox)</li> </ul>
Category C: Severely Symptomatic
Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP (which is a category B condition)
<ul style="list-style-type: none"> <li>▶ Serious bacterial infections, multiple or recurrent (ie, any combination of at least two culture-confirmed infections within a 2-year period) of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and in-dwelling catheter-related infections)</li> <li>▶ Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)</li> <li>▶ Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)</li> <li>▶ Cryptococcosis, extrapulmonary</li> <li>▶ Cryptosporidiosis or isosporiasis with diarrhea persisting <math>&gt; 1</math> month</li> <li>▶ Cytomegalovirus disease with onset of symptoms at age <math>&gt; 1</math> month (at a site other than liver, spleen, or lymph nodes)</li> <li>▶ Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): 1) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; 2) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by CT or MRI (serial imaging is required for children <math>&lt; 2</math> years of age); 3) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance</li> <li>▶ HSV infection causing a mucocutaneous ulcer that persists for <math>&gt; 1</math> month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child <math>&gt; 1</math> month of age</li> <li>▶ Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)</li> <li>▶ Kaposi's sarcoma</li> <li>▶ Lymphoma, primary, in brain</li> <li>▶ Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic</li> </ul>

Modified from Centers for Disease Control. 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 4.** Association of Baseline CD4+ Lymphocyte Percentage With Long-term Risk of Mortality in the NICHD IVIG Clinical Trial

Baseline CD4+ Percentage	Number of Deaths	Number of Patients <sup>a</sup>	Percent Mortality <sup>b</sup>
$\geq 35\%$	30	92	33
30-34%	5	48	10
25-29%	15	49	31
20-24%	13	52	25
15-19%	18	41	44
10-14%	13	30	43
5-9%	22	29	76
$< 5\%$	32	33	97

<sup>a</sup> Includes 374 patients with baseline CD4 percentage data available.

<sup>b</sup> Mean follow-up, 5.1 years.

Derived from Mofenson L, Korelitz J, Meyer WA, et al. *J Infect Dis* 1997;175:1029-1038.

PACTG 152 correlating baseline virologic data with risk for disease progression or death during study follow-up (Table 7).<sup>39</sup> In this study, the relative risk of disease progression was reduced by 54% for each 1 log<sub>10</sub> decrease in baseline HIV RNA level. Disease progression was documented in 11% of children younger than 30 months at the time the study was initiated (mean age, 1.1 years) who had baseline RNA in the lowest quartile (eg, undetectable to 150 000 copies/mL) and in 52% of those with baseline RNA in the highest quartile (eg,  $> 1\,700\,000$  copies/mL).<sup>39</sup> In children age 30 months and older at the time the study was initiated (mean age, 7.3 years), none of those with baseline RNA in the lowest quartile (eg, undetectable to 15 000 copies/mL) compared with 34% of those in the highest quartile (eg,  $> 150\,000$  copies/mL) had disease progression; children with RNA levels in the middle two quartiles (ie, 15 001-50 000 and 50 001-150 000 copies/mL) had similar progression rates (13% and 16%, respectively). The data from children age 30 months and older 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 to 20 000 copies/mL.<sup>6</sup>

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 only moderate.<sup>38</sup> 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 rapid disease progression and those who do not.<sup>35</sup> Additional data indicate that CD4+ T-lymphocyte percentage and HIV RNA copy number at baseline and changes in these parameters over time contribute to prediction of mortality risk in infected children, and the use of the two markers together may define prognosis more accurately.<sup>38,39</sup> Similar data and conclusions have been reported recently from several studies of infected adults.<sup>40-42</sup>

#### Methodologic Considerations in Interpreting and Comparing HIV RNA Assays

Most of the published data regarding HIV RNA in children have been obtained using frozen, stored

**TABLE 5.** Association of Baseline HIV RNA Copy Number With Long-term Risk of Mortality in the NICHD IVIG Clinical Trial

Baseline HIV RNA (Copies/mL) <sup>a</sup>	Number of Deaths	Number of Patients <sup>b</sup>	Percent Mortality <sup>c</sup>
Undetectable (<4000)	6	25	24
4001–50 000	19	69	28
50 001–100 000	5	33	15
100 001–500 000	29	72	40
500 001–1 000 000	8	20	40
>1 000 000	25	35	71
Total	92	254	36

<sup>a</sup> Tested by the NASBA HIV-1 RNA QT Amplification System (Organon Teknika Corporation, Durham, NC) on frozen stored serum.

<sup>b</sup> Mean age, 3.4 years.

<sup>c</sup> Mean follow-up, 5.1 y.

Derived from 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;175:1029–1038.

**TABLE 6.** Association of Baseline HIV RNA Copy Number and CD4+ Cell Percentage With Long-term Risk of Mortality in the NICHD IVIG Clinical Trial

Baseline HIV RNA <sup>a</sup> (Copies/mL)	Baseline CD4+ Cell Percentage	Number of Deaths	Number of Patients <sup>b</sup>	Percent Mortality <sup>c</sup>
≤100 000	≥15%	15	103	15
>100 000	≥15%	32	89	36
≤100 000	<15%	15	24	63
>100 000	<15%	29	36	81

<sup>a</sup> Tested by the NASBA HIV-1 RNA QT Amplification System (Organon Teknika Corporation, Durham, NC) on frozen stored serum.

<sup>b</sup> Mean age, 3.4 y.

<sup>c</sup> Mean follow-up, 5.1 y.

Derived from 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;175:1029–1038.

plasma and serum specimens. Some degradation of HIV RNA occurs with specimen storage or 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 (eg, specimens obtained for patient care). Additionally, the HIV RNA assays used 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 in infected infants and children.

The use of HIV RNA assays for clinical purposes requires specific considerations,<sup>43</sup> which are discussed more completely in the Report of the NIH Panel to Define Principles of Therapy of HIV Infection.<sup>5</sup> 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<sub>10</sub>) or more. For

**TABLE 7.** Association of Baseline HIV RNA Quartile by Age at Entry With Risk of Disease Progression or Death During Study Follow-up in HIV-infected Children Enrolled in PACTG 152

Approximate Quartiles of Baseline HIV RNA (Copies/mL) <sup>a</sup>	Number With Disease Progression or Death	Number Patients	Percent With Disease Progression or Death
Age <30 months at entry <sup>b</sup>			
<1000–150 000	9	79	11%
150 001–500 000	13	66	20%
500 001–1 700 000	29	76	38%
>1 700 000	42	81	52%
Age ≥30 months at entry <sup>c</sup>			
<1000–15 000	0	66	0%
15 001–50 000	7	54	13%
50 001–150 000	13	80	16%
>150 000	22	64	34%

<sup>a</sup> Tested by the NASBA HIV-1 RNA QT Amplification System (Organon Teknika Corporation, Durham, NC) on frozen stored plasma.

<sup>b</sup> Mean age, 1.1 y.

<sup>c</sup> Mean age, 7.3 y.

Derived from Palumbo P, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA.* 1998;279:756–761.

example, plasma RNA measured by the quantitative PCR assay (Amplicor HIV-1 Monitor, Roche Diagnostics Systems, Branchburg, NJ) yields absolute values approximately twice (0.3 log<sub>10</sub>) those obtained using a signal amplification, branched-chain DNA assay (Quantiplex, Chiron Corporation, Emeryville, CA).<sup>6,44,45</sup> Similarly, plasma RNA measured by the nucleic acid sequence-based amplification assay (NASBA, Organon Teknika, Malvern, PA) yields absolute values approximately twice those obtained using the Quantiplex assay but relatively comparable values with the Amplicor HIV-1 Monitor assay.<sup>44–46</sup> Therefore, one HIV RNA assay method should be used consistently for monitoring each individual patient. Choice of HIV RNA assay, particularly in young children, may be influenced by the amount of blood required for the assay. The NASBA assay requires the least amount of blood (100 μL of plasma), followed by the Amplicor HIV-1 Monitor (200 μL of plasma), and the Quantiplex assays (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<sub>10</sub>) in either direction over the course of a day or on different days.<sup>6,42,47</sup> 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.<sup>23,36–38</sup> This decline is most rapid during the first 12 to 24 months after birth, with an average decline of ~0.6 log<sub>10</sub> per year; a slower decline continues until approximately 4 to 5 years of age (average decline of 0.3 log<sub>10</sub> 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 younger than 2 years of and greater than threefold ( $0.5 \log_{10}$ ) in children age 2 years and older after repeated testing should be viewed as reflecting a biologically and clinically significant change. To reduce the impact of assay variability in the clinical management of patients, two samples at baseline can be obtained and the average of the two values used for comparison with future tests. Additionally, 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 a specialist in pediatric HIV infection.

### Specific Issues in Antiretroviral Therapy for HIV-infected Adolescents

Adult guidelines for antiretroviral therapy are appropriate for postpubertal adolescents who were infected sexually or via intravenous drug use during adolescence because such HIV-infected adolescents follow a clinical course that is more similar to that in adults than to that in children.<sup>6</sup> The immunopathogenesis and virologic course of HIV infection in adolescents is being defined. Most adolescents have been infected during their teen-age years and are in an early stage of infection, making them ideal candidates for early intervention. A limited but increasing number of adolescents with HIV infection are long-term survivors of HIV infection acquired perinatally or via blood products as young children. Such adolescents may have a unique clinical course that differs from adolescents infected later in life.<sup>48</sup> 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 and OI should be prescribed according to Tanner staging of puberty and not on the basis of age.<sup>28</sup> Adolescents in early puberty (Tanner stages I and II) should be administered doses using pediatric schedules, whereas those in late puberty (Tanner stage V) should follow adult dosing schedules. Youth who are in the midst of their growth spurt (ie, in females, Tanner stage III and in males, Tanner stage IV) should be monitored closely for medication efficacy and toxicity when using adult or pediatric dosing guidelines.

Puberty is a time of somatic growth and gender differentiation, with females developing more body fat and males more muscle mass. Although theoretically these physiologic changes 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 significant impact has been noted with nucleoside analogue reverse transcriptase inhibitor (NRTI) antiretroviral drugs.<sup>49</sup> Clinical experience with PI and nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) antiretroviral drugs is more limited.

### Specific Issues of Adherence for HIV-infected Children and Adolescents

Advances in the therapy of HIV infection have been accompanied by increasing complexity of therapeutic regimens. Families are faced with new challenges associated with the administration of complex, round-the-clock, medication regimens. Nonadherence with drug therapy is a common problem in the management of acute and chronic illnesses. Nonadherence to prescribed medications has been documented by objective measures and self-reporting in children with a variety of illnesses, including life-threatening conditions such as cancer and renal transplants.<sup>50</sup> Rates of reported adherence to medications administered for the treatment of chronic illnesses have ranged from 11% to 83% in a variety of studies.<sup>50,51</sup>

Lack of adherence to prescribed regimens and subtherapeutic levels of antiretroviral medications may enhance the development of drug resistance.<sup>52</sup> Data indicate that the development of resistance to one of the available PI antiretrovirals may reduce susceptibility to some or all of the other available PI drugs, thus substantially reducing subsequent treatment options. Therefore, education of infected children and their caregivers regarding the importance of compliance with the prescribed drug regimen is necessary at the time of initiation of therapy and should be reinforced during subsequent visits. Many strategies can be used to increase medication adherence, including intensive patient education over the course of 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.<sup>53-55</sup>

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. Additionally, 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. Lack of palatability of such formulations can be problematic depending on the child's willingness and ability to accept and retain the medication. Innovative techniques have been used to increase palatability of medications. These include 1) mixing liquid formulations with milk, chocolate milk, vanilla or chocolate pudding, or ice cream; 2) dulling the taste buds before administration of the drug by chewing ice, giving popsicles, or spoonfuls of partially frozen orange or grape juice concentrates; 3) coating the mouth with peanut butter before administration of the drug; and 4) administering strong-tasting foods such as maple syrup, cheese, or strong-

flavored chewing gum immediately after the drug is given.

In addition, many other barriers to adherence to drug regimens exist for children and adolescents with HIV infection. For example, lack of disclosure creates 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 mid-day doses when the parent is away from the home or the child is at school.

Failure to adhere to prescribed treatment is often viewed as a patient or family problem. However, it may be helpful to change perspective and view adherence as a collaborative effort between the health care provider and the child's family.<sup>53</sup> A comprehensive assessment of adherence issues should be instituted for all children for whom antiretroviral treatment is considered; evaluations should include nursing, social, and behavioral assessments. Additionally, intensive follow-up is required 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 (eg, a safe physical environment and adequate food and housing) may take precedence 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.<sup>53,56,57</sup>

HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and the psychosocial needs of HIV-infected adolescents, who frequently are inexperienced with health care systems. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include 1) denial and fear of their HIV infection, 2) misinformation, 3) distrust of the medical establishment, 4) fear and lack of belief in the effectiveness of medications, 5) low self-esteem, 6) unstructured and chaotic lifestyles, and 7) 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.<sup>58</sup>

Developmental issues make caring for adolescents unique. The adolescent's approach to illness often is different from that of adults. Concrete thought processes make it difficult to take medications when adolescents are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time in life when adolescents do not want to be different from their peers. Additional difficulties face adolescents who live with a parent to whom the adolescent has not yet disclosed his

or her HIV status and to those who are homeless and have no place to store medicine.<sup>57</sup>

## ANTIRETROVIRAL DRUGS

As of January 1998, there were 11 antiretroviral agents approved for use in HIV-infected adults and adolescents in the United States; 6 of these (denoted by an asterisk) have an approved pediatric treatment indication. The agents available fall into three major classes: 1) NRTI agents (ZDV\*, didanosine\* [ddI], stavudine\* [d4T], lamivudine\* [3TC], and zalcitabine [ddC]); 2) NNRTI agents (nevirapine [NVP] and delavirdine [DLV]); and 3) PI agents (saquinavir [SQV] hard and soft gel capsules, indinavir [IDV], ritonavir\* [RTV], and nelfinavir\* [NFV]).

NRTI agents are potent inhibitors of the HIV reverse transcriptase enzyme, which is responsible for the reverse transcription of viral RNA into DNA; this process occurs before integration of viral DNA into the chromosomes of the host cell. NRTI agents require intracellular phosphorylation to their active forms by cellular kinases. The phosphorylated drug acts to competitively inhibit viral reverse transcriptase and to terminate additional elongation of viral DNA after its incorporation into the DNA chain. Because these drugs act at a preintegration step in the viral life cycle, they have little to no effect on chronically infected cells in which proviral DNA has already been integrated into cellular chromosomes. NNRTI agents specifically inhibit reverse transcriptase activity by binding directly to the active site of the enzyme without previous activation. PI agents inhibit the HIV protease enzyme that is required to cleave viral polyprotein precursors and to generate functional viral proteins. The protease enzyme is crucial for the assembly stage of viral replication that occurs after transcription of proviral DNA to viral RNA and subsequent translation into viral proteins. Because PI agents act at a postintegration step of the viral life cycle, they are effective in inhibiting replication in both newly infected and chronically infected cells.<sup>59</sup>

The following summarizes information about antiretroviral drugs currently approved. Table 8 presents information about dosage, toxicities, drug interactions, and special considerations relevant to each specific antiretroviral agent.

### NRTI Agents

NRTI agents were the first class of antiretroviral drugs available for the treatment of HIV infection. Although resistance eventually develops to these agents during the course of long-term, single-drug therapy, combination therapy with these drugs may prevent, delay, or reverse the development of resistance.<sup>60</sup> This class of drugs generally is well tolerated with prolonged use, and toxicities associated with these drugs usually can be managed while continuing to administer therapy.

#### ZDV (AZT, *Retrovir*)

ZDV was the first NRTI studied in adult and pediatric clinical trials and the first antiretroviral agent approved for therapy of HIV infection. Pediatric tri-

**TABLE 8. Drugs Used in Pediatric HIV Infection<sup>a</sup>**

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
<b>NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITOR (NRTI) AGENTS</b>				
Didanosine (ddI) (dideoxyinosine) 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	Neonatal dose (infants <90 d): 50 mg/m <sup>2</sup> q 12h Pediatric usual dose: in combination with other antiretrovirals, 90 mg/m <sup>2</sup> q 12h Pediatric dosage range: 90 to 150 mg/m <sup>2</sup> q 12h (Note: may need higher dose in patients with CNS disease) Adolescent/adult dose: ≥60 kg, 200 mg bid <60 kg, 125 mg bid	Most frequent: diarrhea, abdominal pain, nausea, vomiting Unusual (more severe): peripheral neuropathy (dose related), electrolyte abnormalities, hyperuricemia Uncommon: pancreatitis (dose related, less common in children than adults); increased liver enzymes, retinal depigmentation	Possible decrease in absorption of ketoconazole, itraconazole, dapson; administer at least 2 h before or 2 h after ddI Tetracycline and fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets); administer 2 h before or 2 h after ddI Concomitant administration of ddI and delavirdine (DLV) may decrease the absorption of these drugs; separate dosing by at least 2 h Administration with protease inhibitor (PI) agents: indinavir (IDV) should be administered at least 1 h apart from ddI on an empty stomach. Ritonavir (RTV) should be administered at least 2 h before or after ddI.	ddI formulation contains buffering agents or antacids Food decreases absorption; administer ddI on an empty stomach (1 h before or 2 h after a meal). Additional evaluation in children regarding administration with meals is under study. For oral solution: shake well and keep refrigerated; admixture stable for 30 days When administering chewable tablets, at least two tablets should be administered to ensure adequate buffering capacity (eg, 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 Tablets: COMBIVIR (150 mg lamivudine in combination with 300 mg zidovudine)	Neonatal dose (infants <30 d): 2 mg/kg bid Pediatric dose: 4 mg/kg bid Adolescent/adult dose: ≥50 kg: 150 mg bid <50 kg: 2 mg/kg bid	Most frequent: headache, fatigue, nausea, diarrhea, skin rash, abdominal pain Unusual (more severe): pancreatitis (primarily seen in children with advanced HIV infection receiving multiple other medications), peripheral neuropathy, decreased neutrophil count, increased liver enzymes	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, reversion to phenotypic ZDV sensitivity may be observed	Can be administered with food For oral solution, store at room temperature Decrease dosage in patients with impaired renal function
Stavudine (d4T) ZERT Preparations: Solution, 1 mg/mL Capsules, 15, 20, 30, and 40 mg	Neonatal dose: Under evaluation in PACTG 332 Pediatric dose: 1 mg/kg q 12h (up to body weight of 30 kg) Adolescent/adult dose: ≥60 kg, 40 mg bid <60 kg, 30 mg bid	Most frequent: headache, gastrointestinal disturbances, skin rashes Uncommon (more severe): peripheral neuropathy, pancreatitis Other: increased liver enzymes	Drugs that decrease renal function could decrease clearance Should not be administered in combination with ZDV (poor antiviral effect)	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; available through compassionate use program) Tablets, 0.375 mg and 0.75 mg	Neonatal dose: Unknown Pediatric usual dose: 0.01 mg/kg q 8h Pediatric dosage range: 0.005 to 0.01 mg/kg q 8h Adolescent/adult dose: 0.75 mg tid	Most frequent: headache, gastrointestinal disturbances, malaise Unusual (more severe): peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, skin rashes	Cimetidine, amphotericin, foscarnet, and aminoglycosides may decrease renal clearance of zalcitabine Antacids decrease absorption of zalcitabine Concomitant use with ddI is not recommended because of the increased risk of peripheral neuropathy Intravenous pentamidine increases the risk of pancreatitis (do not use concurrently)	Administer on an empty stomach (1 h before or 2 h 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 Tablets: COMBIVIR (300 mg zidovudine in combination with 150 mg lamivudine) Concentrate for injection, for intravenous infusion: 10 mg/mL	Dose in premature infants: (standard neonatal dose may be excessive in premature infants) Under study in PACTG 331: Oral or IV 1.5 mg/kg q 12h from birth to 2 w of age; then increase to 2 mg/kg q 8h after 2 w of age Neonatal dose: Oral, 2 mg/kg q 6h Intravenous, 1.5 mg/kg q 6h Pediatric usual dose: Oral, 160 mg/m <sup>2</sup> q 6h	Most frequent: hematologic toxicity (including granulocytopenia and anemia), headache Unusual: myopathy, myositis, liver toxicity	Increased toxicity may be observed with concomitant administration of the following drugs (therefore, more intensive toxicity monitoring may be warranted): ganciclovir, interferon-alpha, trimethoprim-sulfamethoxazole, acyclovir, and other drugs that can be associated with bone marrow suppression The following drugs may increase ZDV concentration (and potential toxicity): methadone, atovaquone, valproic acid, probenecid, and fluconazole Decreased renal clearance may be observed with coadministration of cimetidine (may be significant in patients with renal impairment). Fluconazole interferes with metabolism and clearance of ZDV (increases ZDV AUC).	Can be administered with food, although the manufacturer recommends that ZDV be taken 30 min before or 1 h 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 filgrastim, erythropoietin or reduced ZDV dosage may be necessary in some patients Reduced dosage may be indicated in patients with substantial hepatic dysfunction

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
	Intravenous (intermittent infusion), 120 mg/m <sup>2</sup> q 6h Intravenous (continuous infusion), 20 mg/m <sup>2</sup> /h Pediatric dosage range: 90 mg/m <sup>2</sup> to 180 mg/m <sup>2</sup> q 6–8h Adolescent/adult dose: 200 mg tid or 300 mg bid		ZDV metabolism may be increased with coadministration of rifampin and rifabutin (clinical significance unknown); clarithromycin may decrease concentration of ZDV probably by interfering with absorption (preferably administer 4 h apart). Ribavirin decreases the intracellular phosphorylation of ZDV (conversion to active metabolite) Phenytoin may increase or decrease ZDV levels Should not be administered in combination with D4T (poor antiretroviral effect)	Infuse intravenous loading dose or intermittent infusion dose over 1 h. For intravenous solution, dilute with 5% dextrose injection solution to concentration ≤4 mg/mL; refrigerated diluted solution stable for 24 h. Some Working Group participants use a dose of 180 mg/m <sup>2</sup> q 12h when using in drug combinations with other antiretroviral compounds, but data on this dosing in children are limited.
<b>NON-NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI) AGENTS</b>				
Delavirdine (DLV) RESCRIPTOR Preparations: Tablets, 100 mg	Neonatal dose: Unknown Pediatric dose: Unknown Adolescent/adult dose: 400 mg tid	Most frequent: headache, fatigue, gastrointestinal complaints, rash (may be severe).	Metabolized in part by hepatic cytochrome P450 3A (CYP3A); potential for multiple drug interactions <sup>c</sup>  Before administration, the patient's medication profile should be reviewed carefully 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 (eg, astemizole or terfenadine); sedative-hypnotics (eg, alprazolam, midazolam, or triazolam); calcium channel blockers (eg, 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 (eg, phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.  Decreased absorption of DLV if given with antacids or histamine <sub>2</sub> receptor antagonists.  Increased trough concentrations of DLV by ~50% if given with ketoconazole, fluoxetine; increased levels of both drugs if DLV given with clarithromycin  DLV may increase dapsone and quinidine plasma concentrations  Administration with PI agents: decreases metabolism of saquinavir (SQV) and indinavir (IDV), resulting in a significant increase in SQV and IDV concentrations and a slight decrease in DLV concentration	Can be administered with food  Should be taken 1 h before or 1 h after ddi or antacids Tablets can be dissolved in water and the resulting dispersion should be taken promptly
Nevirapine (NVP) VIRAMUNE Preparations: Suspension, 10 mg/mL (investigational; available through compassionate use program)	Neonatal dose (through 3 months): Under study in PACTG 356, 5 mg/kg once daily for 14 days, followed by 120 mg/m <sup>2</sup> q 12h for 14 days, followed by 200 mg/m <sup>2</sup> q 12h Pediatric dose: 120 to 200 mg/m <sup>2</sup> q 12h	Most frequent: skin rash (some severe and life-threatening, including Stevens-Johnson syndrome), sedative effect, headache, diarrhea, nausea  Unusual: elevated liver enzymes, rarely hepatitis	Induces hepatic cytochrome P450 3A (CYP3A); autoinduction of metabolism occurs in 2–4 weeks with a 1.5–2 fold increase in clearance. Potential for multiple drug interactions. <sup>c</sup>  Before administration, the patient's medication profile should be reviewed carefully for potential drug interactions	Can be administered with food Can be administered concurrently with ddl For investigational suspension: must be shaken well; store at room temperature

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
Tablets, 200 mg, scored	Initiate therapy with 120 mg/m <sup>2</sup> given once daily for 14 d. Increase to full dose administered q 12h if no rash or other untoward effects. Adolescent/adult dose: 200 mg q 12h Initiate therapy at half dose for the first 14 d. Increase to full dose if no rash or other untoward effects.		Drugs having suspected interactions should only be used 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 (eg, triazolam or midazolam); oral anticoagulants; digoxin; phenytoin; or theophylline. The metabolism of these drugs may be increased when given with NVP. Administration with PI agents: decreases IDV and SQV concentrations significantly; may also decrease RTV concentration. Not known if increased doses of PI agents are needed.	NVP-associated skin rash usually occurs within the first 6 w 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 (ie, fever, oral lesions, conjunctivitis, or blistering).
<b>PROTEASE INHIBITOR (PI) AGENTS<sup>a,b,c</sup></b>				
Indinavir (IDV) CRIVIVAN Preparations: Capsules, 200 and 400 mg	Neonatal dose: Unknown; because of side effect of hyperbilirubinemia, should not be given to neonates until additional information available Pediatric dose: Under study in clinical trials, 500 mg/m <sup>2</sup> q 8h Adolescent/adult dose: 800 mg q 8h	Most frequent: nausea, abdominal pain, headache, metallic taste, dizziness, 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. Possible association with fat redistribution with and without serum lipid abnormalities. (Causal association not definitively established.)	Cytochrome P450 3A4 responsible for metabolism. Potential for multiple drug interactions. <sup>f</sup> Before administration, the patient's medication profile should be reviewed carefully for potential drug interactions. IDV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. IDV is not recommended for concurrent use with antihistamines (eg, astemizole or terfenadine); cisapride; ergot alkaloid derivatives; or sedative-hypnotics (eg, triazolam or midazolam). IDV levels are significantly reduced with concurrent use of rifampin. Concurrent use is not recommended. Rifabutin concentrations are increased and a dose reduction of rifabutin to half the usual daily dose is recommended Ketoconazole and itraconazole cause an increase in IDV concentrations (consider reducing adolescent/adult IDV dose to 600 mg q 8h) Coadministration of clarithromycin increases serum concentration of both drugs (dosing modification not needed) Coadministration with NVP may decrease IDV serum concentrations Administration with other PI agents: co-administration with NVP increases concentration of both drugs; co-administration with saquinavir (SQV) increases concentration of SQV	Administer on an empty stomach 1 h before or 2 h after a meal (or can take with a light meal) Adequate hydration (at least 48 ounces/day in adult patients) required to minimize risk of nephrolithiasis If coadministered with ddI, give at least 1 h 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 (NFV) VIRACEPT Preparations: Powder for oral suspension, 50 mg per 1 level scoop (200 mg per 1 level teaspoon)	Neonatal dose: Under study in PACTG 353: 10 mg/kg tid (note: no preliminary data available, investigational) Pediatric dose: 25 to 30 mg/kg q 8h	Most frequent: diarrhea Less common: asthenia, abdominal pain, rash, and exacerbation of chronic liver disease	NFV is in part metabolized by cytochrome P450 3A4 (CYP3A4). Potential for multiple drug interactions. <sup>f</sup> Before administration, the patient's medication profile should be reviewed carefully for potential drug interactions.	Administer with food to optimize absorption If coadministered with ddI, NFV should be administered 2 h before or 1 h after ddI

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
Tablets, 250 mg	Adolescent/adult dose: 750 mg tid	Rare: spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, and diabetes. Possible association with fat redistribution with and without serum lipid abnormalities. (Causal association not definitively established.)	NFV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. NFV is not recommended for concurrent use with antihistamines (eg, astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (eg, quinidine or amiodarone); or sedative-hypnotics (eg, triazolam or midazolam). Rifampin significantly decreases NFV concentrations and should not be coadministered Rifabutin causes less decline in NFV concentrations; if coadministered with NFV, rifabutin should be reduced to half the usual dose Estradiol levels are reduced by NFV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control Coadministration with DLV increases NFV concentrations twofold and decreases DLV concentrations by 50%. There are no data on coadministration with NVP, but some experts use higher doses of NFV if used in combination with NVP. Administration with other PI agents: Concomitant administration of IDV and NFV may increase plasma concentrations of both drugs Concomitant administration of SQV and NFV can result in substantially increased plasma concentrations of SQV with little change in NFV concentration Concomitant administration of RTV and NFV increases concentration of NFV without change in RTV concentration	For oral solution: powder may be mixed with water, milk, pudding, or formula (for up to 6 h) Do not mix with any acidic food or juice because of resulting poor taste Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes Tablets disperse readily in water and can be mixed with milk or chocolate milk Tablets can also be crushed and administered with pudding
Ritonavir (RTV) NORVIR Preparations: Oral solution, 80 mg/mL Capsules, 100 mg	Neonatal dose: Under study in PACTG 354 Pediatric dose: 400 mg/m <sup>2</sup> q 12h To minimize nausea/vomiting, initiate therapy at 250 mg/m <sup>2</sup> q 12h and increase stepwise to full dose over 5 d as tolerated Pediatric dosage range: 350 to 400 mg/m <sup>2</sup> q 12h Adolescent/adult dose: 600 mg q 12h (single PI therapy) 400 mg q 12h (in combination with SQV) To minimize nausea/vomiting, initiate therapy at 300 mg q 12h and increase stepwise to full dose over 5 d as tolerated	Most frequent: nausea, vomiting, diarrhea, headache, abdominal pain, anorexia Less common: circumoral paresthesias, increase in liver enzymes Rare: spontaneous bleeding episodes in hemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycemia, diabetes and hepatitis. Possible association with fat redistribution with and without serum lipid abnormalities. (Causal association not definitively established.)	RTV is extensively metabolized in the liver by the cytochrome P450 enzyme 3A (CYP3A). Potential for multiple drug interactions. <sup>c</sup> Before administration, the patient's medication profile should be reviewed carefully for potential drug interactions Not recommended for concurrent use with analgesics (eg, meperidine, piroxicam, or propoxyphene); antihistamines (eg, astemizole or terfenadine); certain cardiac drugs (eg, amiodarone, bepridil hydrochloride, encainide hydrochloride, flecainide acetate, propafenone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (eg, alprazolam, clorazepate, diazepam, estazolam, flurazepam hydrochloride, midazolam, triazolam, or zolpidem tartrate); certain psychotropic drugs (eg, bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin. Estradiol levels are reduced by RTV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control RTV increases metabolism of theophylline (levels should be monitored, and dose may need to be increased) RTV increases levels of clarithromycin (dose adjustment may be necessary in patients with impaired renal function); desipramine (dose adjustment may be necessary); and warfarin (monitoring of anticoagulant effect is necessary). RTV may increase or decrease digoxin levels (monitoring of levels is recommended).	Administration with food increases absorption If administered with ddI, there should be 2 h between taking each of the drugs Capsules must be kept refrigerated To minimize nausea, therapy should be initiated at a low dose and increased to full dose over 5 d as tolerated For oral solution, recommended that it be kept refrigerated and stored in original container; can be kept at room temperature if used within 30 d. Techniques to increase tolerance in children: mix oral solution with milk, chocolate milk, vanilla or chocolate pudding, or ice cream; dull the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates; coat the mouth by giving peanut butter to eat before the dose; administer strong tasting foods such as maple syrup, cheese, or strong flavored chewing gum immediately after dose

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
Saquinavir (SQV) INVIRASE (hard gel capsule) FORTOVASE (soft gel capsule) Preparations: Hard gel capsules (HGC), 200 mg Soft gel capsules (SGC), 200 mg	Neonatal dose: Unknown Pediatric dose: SGC: under study in PACTG 397: 50 mg/kg tid  Adolescent/adult dose: HGC, 600 mg tid SGC, 1200 mg tid (single PI therapy) 400 mg bid (in combination with RTV)	Most frequent: diarrhea, abdominal discomfort, headache and nausea Rare: spontaneous bleeding episodes of hemophiliacs, hyperglycemia and diabetes. Possible association with fat redistribution with and without serum lipid abnormalities. (Causal association not definitively established.)	Drugs that increase CYP3A activity can lead to increased clearance and therefore lower levels of ritonavir or RTV include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because RTV can affect the metabolism of these drugs as well). Administration with other PI agents: coadministration with SQV and NFV increases concentration of these drugs with little change in RTV concentration  SQV is metabolized by the cytochrome P450 3A (CYP 3A) system in the liver and there are numerous potential drug interactions. <sup>c</sup> Before administration, the patient's medication profile should be reviewed carefully for potential drug interactions SQV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. SQV is not recommended for concurrent use with antihistamines (eg, astemizole or terfenadine); cisapride; ergot alkaloid derivatives, or sedative- hypnotics (eg, midazolam or triazolam). SQV levels are significantly reduced with concurrent use of rifampin (decreases SQV levels by 80%), rifabutin (decreases SQV levels by 40%), and NVP (decreases SQV levels by 25%) SQV levels are decreased by carbamazepine, dexamethasone, phenobarbital, and phenytoin SQV levels are increased by delavirdine (or DLV) and ketoconazole SQV may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be monitored closely for toxicity. Administration with other protease inhibitors: co- administration with IDV, RTV, or NFV increases concentration of SQV with little change in concentration of the other drugs.	Administer with a meal or within 2 h after a meal to increase absorption. Concurrent administration of grapefruit juice increases SQV concentration Sun exposure can cause photosensitivity reactions and sunscreen or protective clothing is recommended Capsules must be kept refrigerated. Once brought to room temperature, capsules should be used within 3 m
<b>ANTIVIRAL AGENTS</b>				
Acyclovir ZOVIRAX Preparations: Oral suspension, 40 mg/mL Capsules, 200 mg  Tablets, 400, 800 mg  Intravenous, 500 mg, 1 g	Dosage depends on indication, route of administration, and immunocompetency  Varicella Pediatric dose: Oral, 20 mg/kg q6h; Intravenous, 500 mg/m <sup>2</sup> q8h Adolescent/adult dose: Oral, 800 mg q6h; Intravenous, 10 mg/kg q8h  Zoster Pediatric dose: Oral, 20 mg/kg q6h; Intravenous, 500 mg/m <sup>2</sup> q8h Adolescent/adult dose: Oral, 800 mg q6h; Intravenous, 10 mg/kg q8h	Most frequent: nausea, diarrhea, headache, rash Uncommon: hematologic toxicity Intravenous: renal toxicity due to crystallization of drug within the renal tubules. Phlebitis at site of injection. Rare: encephalopathy	Probenecid decreases renal excretion Possible neurotoxicity in patients receiving ZDV	Decrease dosage in patients with renal impairment Infusion concentrations of ≤7 mg/mL are recommended. Once diluted for administration, IV solution is stable for 24 h IV administration: infuse slowly over 1 h. Must be accompanied by adequate hydration

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
	Herpes Simplex Pediatric dose: Oral, 20 mg/kg q6h; Intravenous, 250 mg/m <sup>2</sup> q8h Infant (<1 m) dose: Intravenous, 15–20 mg/kg q8h Adolescent/adult dose: Oral, 400 mg q4h while awake (5 times daily); Intravenous, 5 mg/kg q8h; Daily suppressive oral therapy, 400 mg q8h			
Foscarnet FOSCAVIR Preparations: IV solution, 24 mg/mL	CMV Retinitis Induction: 60 mg/kg q8h × 14– 21 d or 90 mg/kg q12h Maintenance: 90 mg/kg (infused over 2 h) qd to maximum dose of 120 mg/kg qd VZV and HSV (severe) (acyclovir- resistant) 40–60 mg/kg q8–12h	Most frequent: renal toxicity, fever, nausea, diarrhea, vomiting, headache Less common: alterations in serum electrolytes; hypocalcemia, hypomagnesemia, hypokalemia Unusual: hypertension, palpitations, EKG changes	Concomitant administration of potentially nephrotoxic drugs such as aminoglycosides or amphotericin B should be avoided Additive toxicity has occurred when administered with pentamidine	Reduce dosage in patients with impaired renal function Use adequate hydration to decrease nephrotoxicity. Monitor serum electrolytes. Administer by slow IV infusion. IV solution, 24 mg/mL can be administered via central line. Dilution to <12 mg/mL if given via peripheral line is necessary.
Ganciclovir CYTOVENE Preparations: Capsules, 250 mg Intravenous, 500 mg vial Intraocular, 1–2 mcg/h	CMV Retinitis Induction: Intravenous: 5 mg/kg q12h × 14–21 d Maintenance: Intravenous: 5 mg/kg qd each day or 6 mg/kg qd × 5 d/w Oral dosage in adults/adolescents, 1000 mg q8h Oral dosage in children using a liquid suspension prepared from IV solution, 30–40 mg/ kg q8h (ACTG 226)	Most frequent: granulocytopenia in up to 40% of immunocompromised patients; thrombocytopenia in up to 20% Less common: anemia, rash, abnormal LFTs, chills, headache, nausea, vomiting, diarrhea, abdominal pain, hematuria, elevated serum creatinine, elevated BUN, pain, and inflammation at injection site	Generalized seizures have been reported in patients receiving ganciclovir and imipenem-cilastatin (Primaxin) together. Do not use concomitantly. Use cautiously with other drugs, such as ZDV or TMP/ SMX, which can cause granulocytopenia or thrombocytopenia. Possible interaction with ZDV leading to lower blood levels of ganciclovir (when given orally) and higher blood levels of ZDV. Blood levels of ddl were increased when given either 2 h before or with oral ganciclovir. Oral and IV ganciclovir have been found to increase ddl AUC and Cmax by 50%–70% (depending on dosage). Ganciclovir blood levels were decreased when ddl was given 2 h before oral ganciclovir. The significance of the interactions between oral ganciclovir and ZDV or ddl is not known. Probenecid increases ganciclovir AUC and decreases renal clearance	Reduce dosage in patients with impaired renal function IV administration, after reconstitution, dilute to ≤10 mg/mL in D5W, NS, Ringers, or lactated Ringers. Infuse over 1 h. Maintain good hydration. In-line filter required. Infusion solution must be used within 24 h. Should be kept refrigerated. Handling and disposal, use caution in handling and preparing ganciclovir solutions. Solutions that are undiluted are alkaline (pH 11). Avoid contact with skin and mucous membranes. Administer oral doses with food to increase absorption.
<b>DRUGS USED IN THE PREVENTION/TREATMENT OF OIs</b>				
Atovaquone MEPRON Preparations: Oral suspension, 150 mg/mL	Treatment of mild PCP: Pediatric dosage range: 10–30 mg/kg/d × 21 d Adults/adolescents, 750 mg q12h × 21 d	Rash (23%); GI effects, frequently causes nausea, vomiting, and diarrhea; headache (17%); insomnia (12%); fever (21%)	Atovaquone is highly bound to plasma proteins; administer cautiously to patients receiving other highly protein-bound drugs Rifampin decreases atovaquone concentrations by 50% (rifabutin may have a similar effect). Atovaquone may increase ZDV concentrations RTV may decrease atovaquone plasma concentrations	Administer with a high-fat meal (increases absorption 3-fold).
Azithromycin ZITHROMAX Preparations: Capsules, 250 mg Oral suspension, 20 mg/mL 40 mg/mL	MAC Prophylaxis: Pediatric dose, 5 mg/kg (max dose 250 mg) qd or 20 mg/kg qw Adult/adolescent, 20 mg/kg (max dose 1200 mg) qw MAC Treatment: Pediatric dose, 10 mg/kg qd	Mostly GI: nausea, vomiting, diarrhea, abdominal pain	RTV may increase serum concentrations of azithromycin 1.5–3-fold. Monitor for side effects. No clinically significant drug interactions have been reported with theophylline, warfarin, or digoxin, but monitor closely	Administer 1 h before or 2 h after a meal. Do not administer with aluminum- and magnesium-containing antacids.

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
<p>Clarithromycin BIAVIN Preparations: Film-coated tablets, 250 mg, 500 mg Oral suspension, 25 mg/mL, 50 mg/mL</p>	<p>MAC Prophylaxis: Pediatric dose, 7.5 mg/kg q12h (max dose 500 mg q12h) Adolescent/adult dose, 500 mg, q12h MAC Treatment: Pediatric dose, 7.5 mg/kg q12h (max dose 500 mg q12h) Adolescent/adult dose, 500 mg q12h</p>	<p>Mostly GI: nausea, vomiting, diarrhea, abdominal pain</p>	<p>Clarithromycin may decrease the metabolism of theophylline, digoxin, oral anticoagulants, terfenadine, and carbamazepine Carbamazepine dosage should be decreased by 20%– 50% when clarithromycin is added (monitor carbamazepine concentrations) RTV increases the AUC of clarithromycin by 77%. In patients with renal impairment, clarithromycin doses may require decreasing Clarithromycin decreases ZDV plasma concentrations, probably by decreasing absorption. Separate dosing by <math>\geq 4</math> h. Clarithromycin may increase AUC of ddI and DLV Clarithromycin may increase rifabutin concentrations Rifabutin may increase clarithromycin AUC concomitant administration of IDV and clarithromycin results in increases in AUC's of both agents</p>	<p>Can be administered without regard to meals Reconstituted suspension should not be refrigerated Dosage reduction in patients with impaired renal function should be considered</p>
<p>Co-trimoxazole TMP/SMX Bactrim, Septra Preparations: Oral suspension, trimethoprim 40 mg/5 mL and sulfamethoxazole 200 mg/5 mL Tablets, SS (single-strength) trimethoprim 80 mg and sulfamethoxazole 400 mg DS (double-strength) trimethoprim 160 mg and sulfamethoxazole 800 mg Parenteral: concentrate for injection, for IV infusion TMP, 16 mg/ml and SMX, 80 mg/ml</p>	<p>PCP Prophylaxis: Pediatric dose, 150/750 mg/m<sup>2</sup>/ d in 2 divided doses three times/w on consecutive days Ages 6–12 year, single dose tablet on 3 consecutive d Adult/adolescent dose, 1 DS tablet qd or one SS tablet qd or one DS tablet three times/w PCP Treatment: Pediatric dose: 20/100 (TMP/SMX) mg/kg/d IV in 4 divided doses Adult/adolescent dose: 10–15/ 50–75 (TMP/SMX) mg/kg/d in 3–4 divided doses</p>	<p>Most common: nausea, vomiting, anorexia, and hypersensitivity skin reactions Uncommon: hypersensitivity reactions including serious skin reactions and fever Rare: hematologic toxicity, including leukopenia, neutropenia, and thrombocytopenia; crystalluria. Hemolysis with G-6-PD deficiency</p>	<p>TMP/SMX may prolong the prothrombin time of patients receiving warfarin therapy TMP/SMX increases lamivudine blood levels (possibly competes for renal tubular secretion); unknown significance Increased hematologic toxicity when administered with ZDV</p>	<p>Reduce dosage in patients with impaired renal function Maintain adequate fluid intake to prevent crystalluria and stone formation IV: dilute each 5 mL of injection with 75–125 mL D5W and infuse over 60–90 min</p>
<p>Dapsone Preparations: Tablets, 25, 100 mg Syrup (compassionate use IND), 2 mg/mL</p>	<p>PCP Prophylaxis: Pediatric dose, 2 mg/kg qd (max dose 100 mg) Adolescent/adult dose, 100 mg qd</p>	<p>Common: dose-related hemolytic anemia and methemoglobinemia, rash, fever, nausea, mild hyperkalemia Hemolysis in patients with G-6-PD deficiency Rare: toxic hepatitis and cholestatic jaundice</p>	<p>Rifampin decreases dapsone levels. May need to increase dapsone dose. Trimethoprim increases dapsone levels and toxicity. DdI may increase incidence of PCP break throughs. DLV increases dapsone plasma concentrations by interfering with metabolism</p>	<p>Protect from light Dispense syrup in amber glass bottles</p>
<p>Pentamidine NEBUPENT Oral Inhalation, 300 mg PENTAM Intravenous, 300 mg vial</p>	<p>PCP Prophylaxis: Aerosolized, 300 mg via Respigard II nebulizer q m Intravenous pediatric dose, 4 mg/kg q2–4 w Adult dose, 4 mg/kg q2–4 w PCP Treatment: Pediatric dose, 4 mg/kg qd Adolescent/adult dose, 4 mg/kg qd</p>	<p>Parenteral therapy common: nephrotoxicity, cough, bronchospasm Uncommon: hypotension, cardiac arrhythmias, hypoglycemia, and thrombocytopenia Rare: pancreatitis The same toxicities can be seen with aerosolized therapy but are less common</p>	<p>Other nephrotoxic drugs would increase the incidence of nephrotoxicity</p>	<p>IV infusion should be administered over at least 60 min to decrease the risk of hypotension</p>

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
<p>Fluconazole DIFLUCAN</p> <p>Preparations: Oral suspension, 10 mg/mL, 40 mg/mL</p> <p>Tablets, 50, 100, 200 mg Injection, 2 mg/mL (in dextrose or saline)</p>	<p>Suppressive therapy: Pediatric dose, 3 mg/kg qd</p> <p>Adolescent/adult dose, 200 mg qd</p> <p>Candidiasis (oral therapy): Pediatric dose, 6 mg/kg q12h–24h</p> <p>Adolescent/adult dose, loading dose: 200 mg × 1 d; maintenance dose, 100–200 mg qd</p> <p>Cryptococcal infections: Pediatric dose, 6–12 mg/kg qd (max dose, 400 mg qd)</p> <p>Adolescent/adult dose, 400 mg qd</p>	<p>Most frequent: nausea, vomiting, abdominal pain, diarrhea</p> <p>Unusual: increased transaminase levels, seizure, liver toxicity, leukopenia</p>	<p>Do not administer with astemizole or terfenadine. Fluconazole may increase concentrations of cyclosporin, warfarin, and phenytoin. Monitor for toxicity.</p> <p>Rifampin increases the metabolism of fluconazole. Consider increasing fluconazole dosage.</p> <p>Fluconazole increases ZDV concentrations (ZDV AUC increased as much as 74%, peak levels increased 84%). Monitor for ZDV side effects.</p>	<p>May be given orally without regard to meals Dosage must be adjusted in patients with impaired renal function</p> <p>IV administration, should be administered once daily at a rate ≤200 mg/h</p> <p>Oral and IV dosages are the same</p>
<p>Itraconazole SPORONOX</p> <p>Preparations: Capsules, 100 mg Oral solution, 10 mg/mL</p>	<p>Suppressive therapy/prophylaxis: Pediatric dose, 2–5 mg/kg q12–24h (capsules)</p> <p>Adolescent/adult dose, 200 mg qd (capsules)</p> <p>Oropharyngeal and esophageal candidiasis: Pediatric dose, oral 5 mg/kg qd (oral solution)</p> <p>Adolescent/adult dose, 100–200 mg qd (oral solution)</p>	<p>Common: GI effects such as nausea, vomiting, diarrhea; rash; fever</p> <p>Less common: headache and dizziness, increased LFTs</p> <p>Rare: hepatitis, hypokalemia</p>	<p>Do not administer with terfenadine or astemizole or cisapride. Itraconazole inhibits the metabolism of these agents and could result in serious arrhythmias. Elevated plasma concentrations of midazolam, triazolam, digoxin, and cyclosporin have occurred when coadministered.</p> <p>Itraconazole should be administered at least 2 h before ddl to ensure adequate absorption of itraconazole</p> <p>Itraconazole causes an increase in IDV concentrations.</p>	<p>Capsules, administer after a full meal to increase absorption</p> <p>Oral solution, administer on an empty stomach to increase absorption</p> <p>Itraconazole oral solution has 60% greater bioavailability compared with capsules</p> <p>Itraconazole oral solution should not be used interchangeably with itraconazole capsules</p>
<p>Ketoconazole NIZORAL</p> <p>Preparations: Tablets, 200 mg</p>	<p>Prophylaxis: Pediatric dose, 5–10 mg/kg q12–24h</p> <p>Adult dose, 200 mg qd</p> <p>Treatment: Pediatric dose, 5–10 mg/kg q12–24h</p> <p>Adult dose, 200–400 mg qd</p>	<p>Common: nausea and vomiting</p> <p>Unusual: increased LFTs</p> <p>Rare: hepatotoxicity</p>	<p>Concomitant administration of drugs that decrease gastric acidity (eg, antacids, H-2 antagonists) decrease the absorption of ketoconazole</p> <p>Ketoconazole should be administered at least 2 h before ddl to ensure adequate absorption of the antifungal. Sucralfate decreases absorption.</p> <p>Rifampin increases the metabolism of ketoconazole (do not coadminister).</p> <p>Ketoconazole decreases the metabolism of terfenadine, astemizole, and cisapride, which has led to adverse cardiovascular effects (do not coadminister).</p> <p>Ketoconazole decreases the metabolism of coumarin, cyclosporin, and corticosteroids. Dosage adjustments may be required. Serum concentrations of phenytoin and theophylline may be altered. Monitoring plasma concentrations is recommended.</p> <p>Ketoconazole increases trough concentrations of DLV by approximately 50%.</p> <p>Ketoconazole causes an increase in IDV concentrations (consider dose reduction of IDV).</p>	<p>Adverse GI effects occur less often when administered with food</p> <p>Drugs that decrease gastric acidity or sucralfate should be administered at least 2 h after ketoconazole</p> <p>Disulfiram reactions have occurred in patients ingesting alcohol</p>
<p>Rifabutin MYCOBUTIN</p> <p>Preparations: Capsules, 150 mg</p>	<p>MAI Prophylaxis: Pediatric dose, 5 mg/kg/qd</p> <p>Adolescent/adult dose, 300 mg qd</p> <p>MAI Treatment: Pediatric dose, 5–10 mg/kg qd</p> <p>Adolescent/adult dose, 300 mg qd</p>	<p>Uveitis with high dose (adults &gt;300 mg/d) especially when combined with clarithromycin</p> <p>Occasional: hepatitis, rash, GI intolerance, leukopenia, thrombocytopenia, Flu-like illness with interrupted therapy, yellow or orange skin discoloration (&lt;1%).</p> <p>Brown–orange discoloration of urine (30%)</p>	<p>The related drug rifampin is a potent inducer of liver enzymes responsible for the metabolism of many drugs. Rifabutin may have similar effects but to a much smaller degree than rifampin.</p> <p>Rifampin increases the metabolism of many drugs including methadone, warfarin, digoxin, oral contraceptives, corticosteroids, dapsone, cyclosporin, theophylline, ketoconazole, and ZDV</p> <p>Plasma levels of rifabutin are increased by clarithromycin and fluconazole</p>	<p>May administer with food in patients with GI intolerance</p> <p>May cause brown–orange color to urine, feces, saliva, sweat, tears, skin</p>

TABLE 8. Continued

Drug	Dosage	Major Toxicities	Drug Interactions	Special Instructions
		Dose-related: polyarthralgias/arthritis syndrome	Rifabutin has been shown to significantly increase the clearance of DLV (do not coadminister). DLV increases serum concentrations of rifabutin. There is potentially a rifabutin/NVP drug interaction (insufficient data)	
<b>ADJUNCTIVE THERAPY</b>				
Epoetin Alfa (erythropoietin human glycoform) recombinant (EPO) EPOGEN, PROCRIT Preparations: IV injection or SC use, 2000 U/mL, 3000 U/mL, 4000 U/mL, 10 000 U/mL	Initial dosage, 100 U/kg IV or SC 3 times weekly for 8–12 w Titrate to response by increasing by 50–100 U/kg every 4–8 w  Dosage range, 100 U/kg to 600 U/kg (individualize therapy to patient response)	Infrequent: headache, fever Rare: flu-like syndrome	Unknown	Epoetin alfa injection should not be diluted further before administration or transferred to other containers and/or admixed with other drugs or IV solutions. Albumin is present as a carrier protein and can adsorb to PVC containers and tubing.
Filgrastim (Granulocyte Colony-Stimulating Factor) (G-CSF) NEUPOGEN Preparations: 300 µg/mL for IV infusion or SC	Initial dosage, 1 µg/kg qd SC Titrate to response by increasing by 1 µg/kg increments at weekly intervals Usual maintenance dose, 1 µg/kg/d Dosage range, 1–5 µg/kg/d	Most frequent: bone pain Occasional: erythema or pain at injection site Rare: anemia, thrombocytopenia, acute febrile dermatosis (Sweet's syndrome), vasculitis	Should not be given within 24 h of chemotherapy	Filgrastim injection may be diluted with dextrose 5% in water (D5W) with or without albumin added. Do not dilute with normal saline because precipitation may occur. Albumin is added to the solution to minimize the absorption of filgrastim to infusion containers or equipment. Addition of albumin is unnecessary when the drug is diluted to a concentration of >15 µg/mL in D5W. Albumin should be added when diluted to concentrations <15 µg/mL in D5W (final concentration of 2 µg/mL or 0.2% of albumin). Infuse filgrastim over 15 to 60 min.

<sup>†</sup>Information in this appendix is not all inclusive. Complete and detailed prescribing information on these drugs is available from the drug companies and should be reviewed by the health care provider before prescribing these drugs.

<sup>a</sup>Adolescents in early puberty (Tanner stage 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 stage III females and Tanner stage IV males) should be monitored closely for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

<sup>b</sup>Data in children are limited, and doses may change as more information is obtained about the pharmacokinetics of these drugs in children.

<sup>c</sup>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 the *Guidelines for Use of Antiretroviral Agents on HIV-Infected Adults and Adolescents*<sup>6</sup> and in prescribing information available from drug companies. These interactions will not be reiterated in this table, and the health care provider should review authoritative prescribing guidelines for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be reviewed carefully for potential drug interactions.

als have established drug dosage for children and demonstrated that administration to infected children is safe and associated with weight gain and improved neurologic status.<sup>61,62</sup> ZDV has good central nervous system (CNS) penetration (cerebrospinal fluid [CSF]/plasma ratio = 0.25)<sup>63</sup> and is the NRTI of choice when treating children with HIV-related CNS disease. Perinatal trial PACTG 076 established that a ZDV prophylactic regimen given during pregnancy and labor and to the newborn reduced the risk of perinatal HIV transmission by nearly 70%.<sup>4</sup> ZDV has been studied extensively in both adult and pediatric trials, initially as monotherapy and, more recently, in combination with other agents. ZDV as monotherapy or in combination trials with other NRTI agents has a modest effect on viral load and CD4+ lymphocyte count; dramatic decreases in viral load and increases in CD4+ count have been observed when ZDV has been combined with another NRTI and a PI. The antiretroviral activity of ZDV as monotherapy is limited by emergence of resistance, which generally occurs after 6 to 12 months of treatment. ZDV resistance is a consequence of a stepwise accumulation of genotypic mutations in the viral reverse transcriptase enzyme at codons 215, 70, 41, 67, and 219. When given in combination with another NRTI such as 3TC, the development of ZDV-resistant virus may take longer to occur.<sup>64</sup> The initial dose of ZDV recommended for pediatric patients was 180 mg/m<sup>2</sup> given 4 times daily. However, PACTG 128 demonstrated that a dose of 90 mg/m<sup>2</sup> given 4 times daily had similar efficacy as the higher dose and was associated with less toxicity.<sup>65</sup> A dose of 160 mg/m<sup>2</sup> of ZDV given 3 times daily was the regimen used in the combination therapy trial PACTG 300; ongoing combination antiretroviral pediatric clinical trials are using a ZDV dose of 180 mg/m<sup>2</sup> given 2 times daily. ZDV generally is well tolerated in children, with its major toxicities being anemia and neutropenia.<sup>62</sup> ZDV is approved for use in infants and children and is available in a pleasant-tasting liquid oral preparation.

#### *DDI (Videx)*

DdI was first evaluated as monotherapy for initial treatment of infected children and as therapy for children who had experienced disease progression while receiving ZDV therapy; the drug was well tolerated and associated with antiviral activity, improvement in CD4+ lymphocyte count, and clinical improvement. Despite lower CSF penetration than ZDV (CSF/plasma ratio ≈ 0.05),<sup>66</sup> improvement in neuropsychometric testing was observed in some patients and was correlated with ddI plasma concentration.<sup>67</sup> Results of long-term follow-up of infected children receiving ddI for a median duration of almost 2 years show that ddI appears safe and is associated with clinical improvement, increase in CD4+ count, and decrease in p24 antigenemia, persisting in some cases for several years.<sup>68</sup> In PACTG 152, ddI (administered either as a single agent or in combination with ZDV) was shown to be superior to ZDV monotherapy as initial therapy for symptom-

atic children older than age 3 months.<sup>69</sup> The accepted dose of ddI based on these studies is 120 mg/m<sup>2</sup> as monotherapy and 90 mg/m<sup>2</sup> as part of combination therapy, given 2 times daily. Genotypic mutations at codons 65, 74, and 184 have been associated with ddI resistance. DdI has rare but clinically significant toxicities such as pancreatitis and peripheral neuropathy. Pancreatitis appears to be dose-related; predisposing factors include a history of pancreatitis, advanced disease, CD4+ lymphocyte count <50 cells/mm<sup>3</sup>, baseline elevation of serum transaminases, and concurrent administration of other drugs known to cause pancreatitis, such as pentamidine.<sup>70</sup> Asymptomatic peripheral retinal depigmentation has been observed in <5% of children receiving ddI, is not associated with loss of vision, and appears to reverse with discontinuation of therapy.<sup>71</sup> Diarrhea has been reported and may be more related to the antacid/buffer with which the drug is formulated than to ddI itself. The standard recommendation (based on adult studies) is that ddI be given on an empty stomach to ensure optimal absorption. Unpublished pharmacokinetic data from PACTG 144 suggest that in children, this restriction may not be necessary. DdI is approved for use in infants and children and is available in a liquid preparation suitable for oral administration.

#### *d4T (Zerit)*

D4T has been approved for use in infants and children based on evidence from controlled trials in adults and on safety and pharmacokinetic data from children. D4T appears to be well tolerated in children at a dose of 1 mg/kg given 2 times daily and is available in a liquid preparation for oral administration. Its most significant toxicity is peripheral neuropathy, but this appears to be more uncommon in children than in adults.<sup>72,73</sup> Elevated hepatic transaminases are seen in about 11% and pancreatitis in 1% of adults enrolled in clinical trials of d4T. D4T can be administered without regard to meals. D4T has been studied in pediatric patients in combination with ddI; no pharmacokinetic interactions were observed and there were no cases of peripheral neuropathy.<sup>74</sup> D4T also has been used clinically in combination with 3TC and ddC. D4T and ZDV should not be co-administered. ZDV is a potent inhibitor of the intracellular phosphorylation of d4T *in vitro*<sup>75</sup>, and at least one adult clinical trial indicates that there also may be *in vivo* antagonism associated with this combination.<sup>76</sup> Many clinicians use d4T as a replacement for ZDV when combination drug regimens are changed. D4T also has been studied in children in combination with a PI; the combination of d4T and RTV produced virologic effects comparable with the triple combination of ZDV, 3TC, and RTV in a 12-week interim analysis from PACTG 338.<sup>77</sup> The concentration of d4T in CSF from a study in 8 pediatric patients after 12 weeks of multiple oral dosing varied between 16% and 97% of plasma concentration.<sup>72</sup> High-level resistance to d4T has been difficult to demonstrate; genotypic mutations at codon 50 and 75 have been reported to be associated with diminished *in vitro* susceptibility to d4T.

### 3TC (Epivir)

As with d4T, 3TC has been approved for use in infants and children based on efficacy studies in adults in conjunction with safety and pharmacokinetic studies in children. It is approved for use in infants older than age 3 months and is available in a liquid preparation that may be given orally with or without food. The recommended dose for children older than 3 months is 4 mg/kg administered 2 times daily, with a maximum dose of 150 mg bid. When 3TC is administered as the only antiretroviral agent, resistance emerges rapidly and is associated with a single genotypic mutation at codon 184; therefore, 3TC should not be administered as monotherapy. 3TC appears to have synergistic activity with other NRTI agents that may result from increased fidelity of HIV's reverse transcriptase and development of fewer resistant mutants.<sup>64</sup> As a result of its twice daily dosing schedule, tolerability, ease of administration, and efficacy, demonstrated in clinical trials using viral load and CD4 measurements as surrogate markers, 3TC is used widely in combination therapy regimens.<sup>78</sup> Like d4T, it can be administered without regard to food. The CSF/plasma ratio in children is relatively low (0.11) compared with that for ZDV (0.25) but higher than that for ddI (0.05).<sup>79</sup> The major reported toxicities are pancreatitis and peripheral neuropathy.<sup>78,79</sup>

### DdC (Hivid)

DdC is not approved for use in children younger than age 13 years and is only available commercially in a tablet preparation. A liquid formulation is available through a compassionate use program of the pharmaceutical company (Hoffmann LaRoche). Initial studies both of ddC monotherapy and of alternating ddC and ZDV therapy in pediatric patients demonstrated evidence of antiretroviral activity, with increase in CD4 lymphocyte count and decrease in p24 antigenemia in some patients; however, IQ scores appeared to fall during ddC monotherapy.<sup>80,81</sup> The combination of ddC and ZDV has been studied in pediatric patients and appears to be well tolerated.<sup>82</sup> The optimum dose of ddC in children has not been defined. In a phase I study, ddC plasma concentrations were lower and drug half-life was shorter in children than in adults given comparable doses, suggesting more rapid clearance of the drug in children.<sup>81</sup> Another pediatric clinical trial, PACTG 138, compared 2 doses of ddC (0.01 vs 0.005 mg/kg given orally every 8 hours) for treatment of infected children with disease progression on ZDV monotherapy.<sup>83</sup> Both doses appeared safe, and no difference in efficacy was observed between the higher- and lower-dose groups. Although uncommon, peripheral neuropathy was observed in some children in this study. Genotypic mutations at reverse transcriptase codons 65, 69, and 184 are associated with ddC resistance. DdC has similar toxicities as ddI; combination with ddI is not recommended because of overlapping genotypic resistance mutations and enhanced risk of peripheral neuropathy and pancreatitis. Rashes and oral ulcerations also have been reported with ddC therapy in children.<sup>80</sup>

### NNRTI Agents

There currently are two NNRTI agents approved for treatment of HIV infection, neither of which have pediatric liquid formulations that are approved for use. This class of drugs rapidly reduces viral load and therefore potentially has utility for preventing infection after accidental exposure to HIV and for preventing perinatal transmission. However, drug resistance develops rapidly after initiation of monotherapy, and cross-resistance is likely between the two drugs in this class.<sup>84</sup> Sustained suppression of viral load has been observed in some patients who have been treated with regimens combining NNRTI and NRTI agents.

### NVP (Viramune)

NVP is a specific and potent inhibitor of HIV reverse transcriptase that does not interfere with nucleoside binding. Unlike nucleoside analogues, it acts directly to inhibit reverse transcriptase activity without the requirement for activation by host cellular enzymes. NVP has potent antiviral activity,<sup>85</sup> but resistance develops rapidly when administered as monotherapy. Genotypic mutations associated with viral resistance to NVP typically occur within 6 weeks of initiation of NVP in situations where viral production is not controlled effectively. High-level resistance has been associated with a single point mutation at codon 181 in the reverse transcriptase gene.<sup>86</sup> Therefore, NVP should be used only in combination with other antiretroviral drugs.<sup>87</sup> The drug is highly lipophilic and widely distributed in the body; CSF/plasma concentration ratio is ~0.45. NVP undergoes extensive hepatic metabolism by way of hepatic cytochrome P450 metabolic enzymes, which NVP itself induces. During the course of the first 2 weeks of administration, the drug experiences increasing clearance and decreasing half-life. Therefore, it is recommended that therapy be initiated with a low dose (120 mg/m<sup>2</sup> given 1 time daily), which is increased to a higher maintenance dose after 2 weeks (120–200 mg/m<sup>2</sup> every 12 hours). Plasma concentrations of concomitantly administered drugs that also are metabolized by the cytochrome P450 enzyme pathway may be altered. NVP clearance in children is greater than that in adults, and clearance in children younger than age 9 years is greater than that in older children.<sup>88</sup> Combination therapy with NVP, ZDV, and ddI in young infected infants has been associated with sustained viral suppression in a small number of children.<sup>89</sup> The most common adverse events reported in adults include mild somnolence, headache, diarrhea, nausea, fever, and skin rashes.<sup>84</sup> Skin rash also has been observed in pediatric patients, although it is less frequent when dose escalation is used to initiate therapy. The skin rash typically presents 4 to 6 weeks after initiating therapy and, in rare cases, progresses to Stevens-Johnson syndrome. A liquid formulation of NVP is available through a compassionate use program of the pharmaceutical company Boeinger-Ingelheim.

### *DLV (Rescriptor)*

This NNRTI is not available in a liquid formulation and has not been studied in pediatric patients. DLV tablets dissolve readily in water to form a dispersion that can be mixed with other liquids for oral administration.

### **PI Agents**

PI agents are potent antiretroviral agents, especially when used in combination with NRTI and/or NNRTI therapy.<sup>90</sup> Resistance has been reported with all PI agents when used as monotherapy and can develop rapidly even with combination therapy in the presence of subtherapeutic drug levels (as can occur when there is not adequate adherence to the prescribed drug regimen). The patterns of mutations are more complex than those observed with NRTI and NNRTI agents. A greater number of genotypic mutation sites can occur, and there is greater variability in the temporal pattern of development of these mutations and in the combination of mutations that lead to drug resistance. The mutation patterns associated with PI resistance overlap; resistance to one drug may result in reduced susceptibility to some or all of the other PI agents currently available. Therapeutic regimens consisting of two PI agents (eg, RTV and SQV or NFV and SQV soft gel capsules) combined with one or two NRTI agents are being evaluated in adults and children; early results are promising, showing potent antiviral activity. However, there are no safety data or appropriate recommendations regarding dosage in children available at this time. The practitioner should consider many factors when weighing the short- and long-term risks and benefits of using PI therapy. Among the most important in this regard is the capacity of the patient and family to maintain adherence to the prescribed regimen.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported in HIV-infected patients treated with any of the currently available PI agents.<sup>91-93</sup> In some cases, diabetic ketoacidosis has occurred, and in some patients who discontinued PI therapy, hyperglycemia has persisted. A causal relationship between PI therapy and these events has not been established, but health care providers should be aware of the possibility of hyperglycemia in patients receiving these drugs and monitor appropriately. Caregivers and patients should be taught to recognize the early symptoms of hyperglycemia to ensure prompt health care if such symptoms develop. There also have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia A and B treated with PI agents.<sup>94</sup> In some patients, additional Factor VIII was given, and in more than half of the reported cases, treatment with PI agents was continued or reintroduced.

### *RTV (Norvir)*

RTV is approved for use in children older than age 3 years in combination with NRTI agents. RTV is

available in a liquid preparation suitable for oral administration and should be given with food at a dose of 400 mg/m<sup>2</sup> every 12 hours. RTV monotherapy is associated with substantial decreases in HIV RNA levels and increases in CD4+ lymphocyte counts,<sup>95,96</sup> but resistance develops with continued use of a single drug.<sup>90</sup> Addition of RTV to established antiretroviral regimens decreased clinical progression significantly and mortality in a 6-month clinical trial in infected adults with advanced disease.<sup>97</sup> The major liabilities of RTV are gastrointestinal toxicity, extremely poor palatability of the liquid preparation, and multiple drug interactions. To reduce gastrointestinal intolerance (primarily nausea and vomiting), RTV should be initiated at a dose of 250 mg/m<sup>2</sup> every 12 hours and increased as tolerated to a dose of 400 mg/m<sup>2</sup> over the course of ~5 days. RTV is a potent inhibitor of the cytochrome P450 enzyme pathway and interferes significantly with the metabolism of several common medications including macrolides and certain antihistamines. One small phase I study in children demonstrated a high rate of gastrointestinal intolerance.<sup>98</sup> However, larger studies (eg, PACTG 338) have shown better tolerance of the drug, particularly when dose escalation is used when initiating therapy; in PACTG 338, ~80% of children were able to tolerate RTV at 24 weeks of therapy.<sup>77</sup> An interim analysis of this study demonstrated that children receiving RTV and one or two NRTI agents had a mean decrease of >1.5 log<sub>10</sub> in viral RNA levels after 12 weeks of therapy. Circumoral paresthesias and taste perversion have been reported in adults receiving the drug. Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have been reported in adults receiving RTV alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevation in patients with underlying hepatitis B or C virus infection. Caution should be exercised when administering RTV to patients with preexisting liver disease. There may be cross-resistance between RTV and IDV, and many isolates resistant to IDV also may be resistant to SQV; use of one of these agents after the failure of another is not recommended routinely unless viral resistance status is known for the specific PI.

### *NFV (Viracept)*

NFV is approved for use in children older than age 2 in combination with NRTI and NNRTI agents. It is available in powder and tablet formulations, both suitable for oral administration. Because the powder and pulverized tablets are not soluble, they should be given either suspended in a beverage (noncitric acid-containing to avoid bitterness) or within a semisolid food (not applesauce). Virologic efficacy of NFV in combination with ZDV and 3TC in children has been established in a study of 12 patients; HIV RNA levels were reduced by >2 logs.<sup>99</sup> When given with two NRTI agents in treatment-naive adults, a mean 1.6 log reduction in HIV RNA copy number was sustained for 24 weeks, with >70% of patients achieving undetectable HIV RNA levels (<400 cop-

ies/mL).<sup>100</sup> Data from a phase I study in children indicate that a dose of 22 to 30 mg/kg 3 times daily yields steady-state plasma concentrations that are approximately equivalent to concentrations achieved in adults at doses of 500 to 750 mg 3 times daily.<sup>101</sup> Dosing schedules for prepubertal children >25 kg are now being evaluated. NFV, like IDV, is prone to numerous drug interactions. It has few toxicities and is, in general, well tolerated in children, with the most common adverse effects being diarrhea, abdominal pain, flatulence, and rash. As with all other PI agents, the long-term safety, durability of virologic efficacy, and feasibility of children taking this drug for long periods are unknown. NFV oral powder contains 11.2 mg phenylalanine per gram of powder, which could be problematic for patients with phenylketonuria. NFV-resistant virus may retain sensitivity to other PI agents because of a distinct pattern of genetic mutation; therefore, changing from NFV to another PI may be effective. However, RTV- or IDV-resistant virus often is also NFV-resistant; therefore, changing from either of these drugs to NFV is not recommended.

#### *IDV (Crixivan)*

IDV is not approved for use in children younger than age 13 and is not available in a liquid preparation. It is being studied in dosage ranges of 300 to 500 mg/m<sup>2</sup> given every 8 hours. In clinical trials in infected adults, IDV in combination with NRTI agents has been shown to retard clinical progression and to decrease mortality and to dramatically reduce HIV RNA levels and increase CD4+ lymphocyte counts compared with dual nucleoside therapy.<sup>102,103</sup> IDV must be taken on an empty stomach 1 hour before meals and is prone to multiple drug interactions because of its interaction with the cytochrome P450 system. Its most serious side effect in adults and children is nephrolithiasis. If signs and symptoms such as flank pain with or without hematuria occur, temporary interruption of therapy (for 1–3 days) during the acute episode may be considered. Adequate hydration is essential when IDV is administered. Additionally, asymptomatic mild elevation of bilirubin also has been reported in adults and children receiving IDV.

#### *SQV (Invirase [Hard Gel Capsule]; Fortovase [Soft Gel Capsule])*

SQV was the first PI approved for use in adults in combination therapy with NRTI agents. In its original formulation, as a hard gel capsule (Invirase), it had very limited bioavailability (≈4%) after oral administration. The drug appears to be well tolerated, with mild gastrointestinal disturbances (diarrhea, nausea, abdominal pain) and reversible elevations in liver function tests being the most common side effects reported in adults. SQV has not been approved formally for use in children and is not yet available in a liquid preparation. Despite the low oral bioavailability of the hard gel capsule form of SQV, the drug has demonstrated virologic efficacy in clinical trials of combination therapy with ZDV and ddC in adults; a 0.8 log decrease in HIV RNA after 48 weeks of

therapy was observed.<sup>104</sup> In a monotherapy regimen of high-dose SQV, the maximum decrease in HIV RNA was 1.3 log.<sup>105</sup> RTV and NFV have been shown to inhibit the metabolism of SQV; plasma levels of SQV are increased when it is co-administered with another PI.<sup>106,107</sup> Combination therapy with RTV and the hard gel capsule formulation of SQV is being used in adults. Although this combination is under study in children, no data are yet available on safety or appropriate dosing. A new soft gel capsule preparation (Fortovase) with significantly enhanced oral bioavailability has been approved recently by the FDA for treatment of infected adults; there are no data available regarding the pharmacokinetics and safety of this formulation in combination with RTV. The new formulation is under study in children and initial pharmacokinetic study results are similar to those in adults.<sup>108</sup> SQV must be taken with meals containing fat to enhance absorption. Resistance to SQV is associated with a unique mutation pattern, and viral isolates resistant to SQV are not necessarily resistant to the other PI agents. However, viral isolates resistant to RTV and IDV usually are also resistant to SQV.

#### **Other Antiretroviral Agents That May Soon Be Approved for Use**

A number of new drugs are being used in combination therapy in clinical trials and may be available in the future for use in infants, children, and adolescents for treatment of HIV infection. The following is a brief summary of these drugs.

Abacavir (1592U89) is an NRTI agent that has been investigated as part of combination therapy in adults and children and is available presently in a liquid formulation for children with HIV infection through a company-sponsored open label protocol. It is expected that this drug will be used in combination therapy for treatment of HIV and will be considered for approval by the FDA in 1998.

Preveon, [adefovir dipivoxil, bis-POM PMEA], is a reverse transcriptase inhibitor but belongs to a new class of antiviral agents called nucleotides. It is an oral drug with a prolonged half-life and is taken 1 time daily. This drug is being studied in clinical trials in adults.

PMPA, {9-[(R)-2-(phosphonomethoxy)propyl]adenine}, is an NRTI agent that has undergone phase I trials in adults. PMPA is administered intravenously; however, an oral prodrug, bis-POC PMPA, has been developed that has a prolonged half-life and is targeted for phase I trials in infants and children.

Sustiva, [efavirenz, DMP 266], is a new NNRTI that can be taken 1 time daily and is being studied in combination therapy. Phase I trials are underway in the pediatric population.

Amprenavir, (141W94/VX-478), is a new PI that is planned for phase I studies in the pediatric population as part of combination therapy for treatment of HIV infection.

Hydroxyurea is an oral drug used for treatment of certain cancers that has strong antiretroviral activity when combined with other drugs such as ddI. This drug has a mechanism of action that differs from that

of other antiretrovirals in that it interferes with DNA formation by inhibiting a cellular enzyme, ribonucleotide reductase, necessary for the formation of special nucleotide units needed to form DNA. Studies of hydroxyurea in children are in the initial phases of development.

In addition to the drugs listed above, there also are new classes of drugs being developed that will work at different points in the viral life cycle. Among these are drugs that block binding of HIV to cells, integrase inhibitors (integrase is an enzyme that integrates the viral genetic material into the host genome) and zinc finger inhibitors (zinc fingers are parts of proteins that bind to nucleic acids and are essential for the assembly of new virus particles).

### 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 pharmacokinetic studies performed in full-term infants.<sup>109</sup> Because ZDV is cleared primarily through hepatic metabolism (ie, glucuronidation), which is immature in neonates, the half-life and clearance of ZDV are prolonged in neonates compared with those in older infants, thus requiring adjustments in dosing.

Premature infants have even greater immaturity in hepatic metabolic function than do full-term infants, and additional prolongation in clearance has been documented in very premature infants (eg, those born before 34 weeks of gestation).<sup>110</sup> Appropriate ZDV dosing for premature infants has not been defined but is being evaluated in a phase I clinical trial in premature infants <34 weeks of gestation (PACTG 331).

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.<sup>111,112</sup> Clearance was prolonged in these infants. Based on data from this study, the dose recommended for newborns is half the dose recommended for older children (Table 8). No data are available regarding 3TC pharmacokinetics in infants 2 to 6 weeks old, and the exact age at which 3TC clearance begins to resemble that in older children is not known.

NVP administration to HIV-infected pregnant women during labor and as a single dose to their newborns at 2 to 3 days of age has been studied in a phase I trial.<sup>113</sup> The half-life of NVP was prolonged in neonates compared with that in older children, indicating that some modification of NVP dosage is required for administration to neonates.

Although phase I studies of several PI agents (ie, IDV, RTV, NFV, or SQV in combination with ZDV and 3TC) in pregnant HIV-infected women and their infants are ongoing in the United States, no data are available at this time regarding drug dosage, safety, and tolerance of any of the PI agents in neonates.

## INITIATION OF ANTIRETROVIRAL THERAPY

### Application of Data From Clinical Trials of Antiretroviral Agents

Therapy with a single NRTI has been shown to provide substantial benefit to symptomatic infected adults compared with no therapy, despite the limited antiretroviral potency of monotherapy compared with current combination regimens. In initial placebo-controlled antiretroviral clinical trials in HIV-infected adults, ZDV monotherapy decreased disease progression and mortality in patients with AIDS as well as in patients with mild symptoms or those with immune suppression but no clinical symptoms.<sup>114–116</sup> In symptomatic pediatric patients, clinical, immunologic, and virologic benefit has been observed with monotherapy with a variety of NRTI agents, including ZDV, ddI, d4T, and 3TC.<sup>61,62,67–69,72,79</sup>

Subsequent comparative clinical trials in clinically or immunologically symptomatic infected adults have demonstrated the superior clinical efficacy of initial therapy with dual NRTI combination antiretroviral regimens compared with NRTI monotherapy.<sup>102,117</sup> Similarly, in pediatric trials in symptomatic, antiretroviral-naïve infected children, initial combination therapy with dual NRTI agents (either ZDV and 3TC or ZDV and ddI) was clinically, immunologically, and virologically superior to initial therapy with a single NRTI.<sup>69,118</sup> More recent studies in antiretroviral-experienced adults have demonstrated that combination therapy that includes a PI (generally with two NRTI agents) is clinically, immunologically, and virologically superior to dual NRTI therapy.<sup>104,119</sup> Recent data from pediatric trials also indicate that therapy that includes a PI is virologically and immunologically superior to a dual NRTI combination in symptomatic antiretroviral-experienced children.<sup>77</sup>

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 observed during the first 1 to 2 years of life after 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 setpoint, and result in improved clinical outcome.

In a preliminary study of early treatment of children, six HIV-infected infants 2 to 4 months of age were placed on a regimen of ZDV, ddI, and NVP; baseline HIV RNA levels were 40 000 to 1 500 000 copies/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.<sup>89</sup> These two children had persistently negative HIV cultures and 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 theoretic problems with early therapy include the potential for short- and long-term adverse effects, particularly for drugs being administered to infants younger than 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. Additionally, 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. Thus, intensive education of caregivers and patients about the importance of adherence to the prescribed treatment regimen should be provided before therapy is initiated so that 1) potential problems and solutions can be identified, and 2) 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 (ie, clinical category A, B, or C) (Table 3) or evidence of immune suppression (ie, immune category 2 or 3) (Table 2), regardless of the age of the child or viral load. Clinical trial data from adults and children have demonstrated that antiretroviral therapy in symptomatic patients slows clinical and immunologic disease progression and reduces mortality.<sup>69,118,120</sup>

Ideally, antiretroviral therapy should be initiated in all HIV-infected infants younger than 12 months as soon as a confirmed diagnosis is established, regardless of clinical status, immunologic status, or viral load. HIV-infected infants younger than 12 months are considered at high risk for disease progression, and the predictive value of immunologic and virologic parameters to identify those 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 to 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 currently available, and information on drug dosing in neonates is limited. Because resistance to antiretroviral drugs (particularly PI agents) 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 were outlined by the Working Group for initiating therapy in asymptomatic

children older than 1 year. The first approach would be to initiate therapy in all HIV-infected children, regardless of age or symptom status. Such an approach would ensure 1) treatment of infected children as early as possible in the course of disease, and 2) intervention before immunologic deterioration. Data from prospective cohort studies indicate that most HIV-infected infants will have clinical symptoms of infection by 1 year of age.<sup>121,122</sup> Additionally, most asymptomatic infected children older than 1 year have CD4+ T-lymphocyte percentages of <25%,<sup>122</sup> which is indicative of immunosuppression and therefore warrants antiretroviral therapy.

An alternative approach would be to defer treatment in asymptomatic children older than 1 year with normal immune status in situations in which the risk of clinically significant disease progression is low (eg, low viral load) and when other factors (eg, concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, the health care provider should monitor virologic, immunologic, and clinical status carefully. Factors that should be considered in deciding when to initiate therapy include 1) high or increasing HIV RNA levels, 2) rapidly declining CD4+ T-cell lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (ie, immune category 2 [Table 2]), and 3) 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 (Tables 5, 6), and antiretroviral therapy should be initiated regardless of clinical or immune status. HIV RNA levels consistent with the current treatment recommendations for HIV-infected adults (ie, >10 000–20 000 copies/mL) also may be indicative of the need for treatment for asymptomatic children 30 months of age and older (Table 7). Additionally, any child with HIV RNA levels that demonstrate a substantial increase (more than a 0.7 log<sub>10</sub> [fivefold] increase for children younger than age 2 and more than 0.5 log<sub>10</sub> [threefold] increase for those 2 years of age and older) 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 (Table 9).

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 PI agents, 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.

**TABLE 9.** Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children<sup>a</sup>

1. Clinical symptoms related to HIV infection (ie, clinical category A, B, or C) (Table 3)
2. Evidence of immune suppression, as indicated by CD4+ lymphocyte absolute number or percentage (ie, immune category 2 or 3) (Table 2)
3. All HIV-infected infants <12 months of age, regardless of clinical, immunologic, or virologic status
4. Asymptomatic HIV-infected children ≥1 year of age with normal immune status:
  - Initiate therapy in all HIV-infected children regardless of age, symptom, immunologic, or virologic status (preferred option)
  - or
  - Defer treatment in situations in which the risk of clinically significant disease progression is low and other factors (eg, concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, clinical, immunologic, and virologic status should be monitored carefully. Factors that should be considered in deciding when to initiate therapy include 1) high or increasing HIV RNA copy number (see text); 2) rapidly declining CD4+ T-lymphocyte number or percentage to values approaching those indicative of moderate immune suppression (ie, immune category 2) (Table 2); and 3) development of clinical symptoms.

<sup>a</sup> Indications for initiation of antiretroviral therapy in HIV-infected adolescents should follow the *Guidelines for Use of Antiretroviral Agents in HIV-infected Adults and Adolescents*.<sup>6</sup>

### Choice of Initial Antiretroviral Therapy

Combination therapy is recommended for all infants, children, and adolescents treated with antiretroviral agents. Compared with monotherapy, combination therapy 1) slows disease progression and improves survival, 2) results in a greater and more sustained virologic response, and 3) delays development of resistant mutations. Monotherapy with the antiretroviral drugs currently available 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 identified as being HIV-infected while receiving ZDV chemoprophylaxis should be changed to a combination antiretroviral drug regimen; ZDV therapy should be interrupted if combination therapy is not initiated immediately and should not be resumed until/unless it is part of a combination regimen.)

Aggressive antiretroviral therapy for primary perinatal infection with three drugs provides the best opportunity to preserve immune function and delay disease progression and thus is recommended. The goal of antiretroviral therapy is to suppress viral replication maximally, preferably to undetectable levels. Based on clinical trials in infected adults, the preferred regimen to accomplish this goal is combination therapy with two NRTI agents and one PI. Although these combinations have had limited evaluation in clinical trials in children, they can reduce HIV RNA to undetectable levels in some children.<sup>77,101,123,124</sup> An interim analysis from a clinical trial of children (ie, PACTG 338) has demonstrated that therapy with drug combinations that include a PI is more effective than therapy with two NRTI antiretroviral drugs in reducing viral load to unde-

tectable levels and increasing CD4+ T-lymphocyte number.<sup>77</sup> 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 likely will become available, which will increase treatment options for children in the future.

PI agents with formulations appropriate for infants and children who cannot swallow pills include NFV, available in a powder formulation that can be mixed with water or food, and RTV, available in liquid formulation. Optimal dosing of these drugs in children younger than 2 years is not known but is being evaluated in clinical trials. IDV and SQV are not available in liquid formulations. IDV or soft gel SQV capsules are recommended for consideration as second-line agent 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. The original hard gel capsule formulation of SQV has limited bioavailability and thus is not recommended for use with two NRTI agents. Some studies have indicated substantial increases in SQV drug levels when co-administered with other PI agents (eg, RTV) or with other drugs that inhibit the cytochrome P450 enzyme system. However, data regarding such combinations in children are not available.

Although not ideal, alternative regimens 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 demonstrated clinical benefit in adult and pediatric patients, although these regimens may not suppress viral load to below-detectable levels as consistently as does combination therapy with two NRTI agents and a PI. Such alternative regimens include combination regimens of two NRTI agents, with NVP substituted for the PI, or two NRTI agents 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.

Table 10 lists the recommended antiretroviral drug regimens for initiation of therapy in a previously untreated child. Table 8 lists the antiretroviral drugs currently available and dosing for infected infants, children, and adolescents, and provides detailed information on toxicities and special instructions for use in children.

The initial antiretroviral regimen chosen for infected infants theoretically could be influenced by the antiretroviral regimen their mothers may have received during pregnancy. However, data from PACTG 076 indicate that ZDV resistance did not account for most infants who became infected despite maternal ZDV treatment,<sup>125</sup> and data from PACTG 185 indicate that duration of previous 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.<sup>126</sup> Data do not suggest that

**TABLE 10.** Recommended Choices of Antiretroviral Agents for Initial Therapy of HIV-infected Children

**Preferred regimen:** Based on evidence of clinical benefit and sustained suppression of HIV RNA in clinical trials in HIV-infected adults; clinical trials in HIV-infected children are ongoing.

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**Two NRTI agents plus one highly active PI**

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Recommended dual NRTI combinations:	Protease inhibitor:
ZDV + ddI <sup>a</sup>	NFV <sup>b</sup>
ZDV + 3TC <sup>a</sup>	RTV <sup>b</sup>
d4T + ddI	IDV <sup>c</sup>
d4T + 3TC	SQV soft gel capsules <sup>c</sup>
ZDV + ddC <sup>d</sup>	

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**Alternative regimens:** NVP<sup>e</sup> + 2 NRTI agents (recommended regimens listed above)

**Secondary alternative regimen:** clinical benefit demonstrated but initial viral suppression may not be sustained. Two NRTI agents (recommended dual combinations listed above)

**Not recommended:** evidence against use because of overlapping toxicity and/or virologic undesirability

- Any monotherapy<sup>f</sup>
- d4T + ZDV
- ddC + ddI
- ddC + d4T
- ddC + 3TC

<sup>a</sup> Most efficacy data available in children.

<sup>b</sup> Preferred PI for infants and children who cannot swallow pills or capsules.

<sup>c</sup> Alternative for children who can swallow pills or capsules.

<sup>d</sup> ddC is not available in a liquid preparation commercially, although a liquid formulation is available through a compassionate use program of the pharmaceutical company (Hoffman-LaRoche). Combination ZDV and ddC is a less preferred choice for use in combination with a PI.

<sup>e</sup> A liquid preparation of NVP is not available commercially, but is available through a compassionate use program of the pharmaceutical company (Boeringer-Ingelheim).

<sup>f</sup> 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.

the antiretroviral regimen for an infected infant 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.

## CHANGING ANTIRETROVIRAL THERAPY

### When to Change Antiretroviral Therapy

Each of the following three circumstances warrants a change in antiretroviral therapy: 1) failure of the current regimen with evidence of disease progression based on virologic, immunologic, or clinical parameters (Table 11); 2) toxicity or intolerance of the current regimen; or 3) new data demonstrating that a drug or regimen is superior to the current regimen.

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

**TABLE 11.** Considerations Relevant to Changing Antiretroviral Therapy in HIV-infected Children<sup>a</sup>

Virologic Considerations <sup>b</sup>
1. Less than a minimally acceptable virologic response after 8–12 weeks of therapy. For children receiving antiretroviral therapy with 2 NRTI agents and a PI, such a response is defined as a <10-fold (1.0 log <sub>10</sub> ) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (ie, dual NRTI combinations), an insufficient response is defined as a <5-fold (0.7 log <sub>10</sub> ) decrease in HIV RNA levels from baseline.
2. HIV RNA not suppressed to undetectable levels after 4–6 months of antiretroviral therapy. <sup>c</sup>
3. Repeated detection of HIV RNA in children who initially responded to antiretroviral therapy with undetectable levels. <sup>d</sup>
4. A reproducible increase in HIV RNA copy number in 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 >3-fold (>0.5 log <sub>10</sub> ) increase in copy number for children ≥2 years of age and a >5-fold (>0.7 log <sub>10</sub> ) increase for children <2 years of age are observed.
Immunologic Considerations <sup>b</sup>
1. Change in immunologic classification (Table 2). <sup>e</sup>
2. For children with CD4+ percentages of <15% (ie, immune category 3), a persistent decline ≥5 percentiles in CD4+ cell percentage (eg, from 15% to 10%).
3. A rapid and extensive decrease in absolute CD4+ T-lymphocyte count decrease (eg, a >30% decline in <6 months).
Clinical Considerations
1. Progressive neurodevelopmental deterioration.
2. Growth failure (ie, persistent decline in weight–growth velocity despite adequate nutritional support and without other explanation).
3. Disease progression (ie, advancement from one pediatric clinical category to another) (Table 3). <sup>f</sup>

<sup>a</sup> Considerations for changing antiretroviral therapy in HIV-infected adolescents should follow the *Guidelines for Use of Antiretroviral Agents in HIV-infected Adults and Adolescents*.<sup>6</sup>

<sup>b</sup> At least two measurements (taken at least 1 week apart) should be performed before considering a change in therapy.

<sup>c</sup> The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5 to 2.0 log<sub>10</sub> fall in HIV RNA copy number, even if RNA remains detectable at low levels.

<sup>d</sup> More frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (eg, if using an HIV RNA assay with a lower limit of detection of 1000 copies/mL, there is a ≤0.7 log<sub>10</sub> increase from undetectable to ~5000 copies/mL in an infant <2 years of age).

<sup>e</sup> Minimal changes in CD4+ percentile that may result in change in immunologic category (eg, from 26% to 24% or 16% to 14%) may not be as much a cause for concern as a rapid substantial change in CD4+ percentile within the same immunologic category (eg, a decrease from 35% to 25%).

<sup>f</sup> 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.

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 admin-

istration 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 persons with HIV infection. 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 currently available HIV RNA assays, which may not always be achievable in children with HIV infection. 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 adults with HIV infection.<sup>6</sup> The recommendations for adults indicate that health care providers should consider changing therapy if 1) 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 2) HIV RNA has not decreased to undetectable levels after 4 to 6 months of therapy. Because HIV RNA levels in perinatally infected infants 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 that observed in adults (ie, 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 NRTI agents and a PI. Therefore, virologic indications for changing therapy in infected children differ slightly from those recommended for infected adults. Adult guidelines should be followed for infected adolescents.<sup>6</sup>

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 onset of therapy. If baseline HIV RNA levels are high (ie,  $>1\,000\,000$  copies/mL), virologic response may not be observed until 8 to 12 weeks after initiating antiretroviral therapy. However, if baseline HIV RNA levels are similar to those observed in untreated infected adults (ie,  $<100\,000$  copies/mL), initial response should be observed within 4 weeks after initiating 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 at least 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 to 12 weeks of therapy. For children receiving antiretroviral therapy with two NRTI agents and one PI, such a response is defined as a less than 10-fold ( $1.0 \log_{10}$ ) decrease from baseline HIV RNA levels. For children who are receiving less potent antiretroviral therapy (ie, 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 to 6 months of antiretroviral therapy. However, although suppression of HIV RNA to undetectable levels and maintenance for prolonged periods is desirable, few data in 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  $\log_{10}$  reduction in HIV RNA copy number, even if RNA remains detectable at low levels.
- Repeated detection of HIV RNA in children who had initially 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 (eg, if using an HIV RNA assay with a lower limit of detection of 1000 copies/mL, there is a  $\leq 0.7 \log_{10}$  increase from undetectable to  $\approx 5000$  copies/mL in an infant younger than age 2). 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 in children who have had a substantial HIV RNA response but who 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 for children 2 years and older and a greater than fivefold ( $>0.7 \log_{10}$ ) increase is observed for children younger than 2 because of the greater biologic variability in RNA in young children.

### Immunologic Considerations for Changing Therapy

CD4+ T-lymphocyte count and percentage are independent predictors of disease progression and mortality in HIV-infected children.<sup>38,39</sup> 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.<sup>38</sup> Additionally, for children with CD4+ percentages  $<15\%$  (ie, those in immune category 3), prognosis was correlated with the degree of depression of CD4+ percentage (ie, life expectancy was lower for children with CD4+ percentages  $<5\%$  compared with children with CD4+ percentages 10%–14%) (Table 4).

Before considering changing antiretroviral therapy because of 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 2). However, minimal changes in CD4+ percentile that may result in a change in immune category (eg, from 26% to 24% or from 16% to 14%) may not be as critical as a rapid substantial change in CD4+ percentile within the same immune category (eg, a decrease from 35% to 25%).
- For children with CD4+ percentages  $<15\%$  (ie, those in immune category 3), a persistent decline of five or more percentiles in CD4+ cell percentage (eg, from 15% to 10% or from 10% to 5%).
- A rapid and extensive decrease in absolute CD4+ T-lymphocyte count (eg, 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 (ie, 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) (Table 12). In such cases, the new treatment regimen should optimally include at least one antiretroviral drug with substantial CNS penetration (eg, ZDV or

**TABLE 12.** Neurodevelopmental Criteria for CNS Disease Progression

<p>HIV-associated neurologic disease progression, in the absence of alternative explanations, can be defined as: 1) the child who is neurologically normal at baseline, subsequently developing <i>one</i> of the following major abnormalities A, B, or C (below); or, 2) the child who possesses neurologic or developmental abnormalities at baseline, subsequently developing <i>two</i> of the following major abnormalities A, B, or C (below).</p>	
A.	<p>Impairment of brain growth, in the absence of alternative etiologies, documented by 1, 2, 3, or 4 and should be persistent or progressive as documented by two measures separated by at least 2 months</p> <ol style="list-style-type: none"> <li>1. For infants <math>&lt;1</math> year of age, failure to attain above the 5th percentile head circumference growth curve (National Center for Health Statistics growth curves), with neither an alternative explanation nor a diagnosis of congenital microcephaly</li> <li>2. For infants <math>&lt;3</math> years of age, crossing 2 major head circumference growth-curve percentiles from a baseline measurement, without alternative explanation. Consider neuroimaging correlation that demonstrates atrophy and basal ganglia calcification.</li> <li>3. For any age, falling below the 5th percentile head circumference growth curve without an alternative explanation. Consider neuroimaging correlations.</li> <li>4. For any age, serial neuroimaging studies, performed under the same conditions and reviewed/compared simultaneously, documenting progressive and significant loss of cerebral parenchymal volume ("atrophy"), without other cause.</li> </ol>
B.	<p>Decline of cognitive function, documented by psychometric testing persistent on at least two individual valid assessments separated by at least 1 month:</p> <ol style="list-style-type: none"> <li>1. For infants from birth to 3 years, a fall of 2 SD units on a standardized, nonscreening developmental assessment (for example, the MDI of the Bayley Scales of Infant Development).<sup>a,b</sup></li> <li>2. For children <math>&gt;3</math> years, a fall of <math>\geq 1</math> SD on a standardized test of intelligence.<sup>b</sup></li> <li>3. At any age, loss of previously attained cognitive or language milestones, without alternative explanation, and confirmed by standardized testing.<sup>a,b</sup></li> </ol>
C.	<p>Clinical motor dysfunction, without alternative explanation, documented to be progressive on two individual examinations separated by at least 1 month in:</p> <ol style="list-style-type: none"> <li>1. loss or significant deterioration of motor skills attained previously. or in any of the following subcriteria 2, 3, or 4.</li> <li>2. Diffuse and symmetric loss or deterioration in power or strength that is not the result of a systemic, nutritional, or metabolic complication.</li> <li>3. Diffuse and symmetric abnormalities of tone, including, but not limited to, hypotonia, hypertonia, or rigidity.</li> <li>4. Diffuse, symmetric, and pathologically increased deep tendon reflexes.</li> </ol>

<sup>a</sup> Scores corrected for prematurity may lead to factitious results. Thus, consider using uncorrected scores for premature infants.

<sup>b</sup> For children who start with developmental delay, or for those transitioning to a different standardized test, consult a psychologist to determine change over time.

- NVP, which have CSF/plasma ratios  $>0.2$ ).
- Growth failure (ie, persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation).
- Disease progression (ie, advancement from one pediatric clinical category to another [Table 2]). Prognosis is poorer as patients progress to more advanced clinical categories.<sup>62</sup> However, in patients with stable immunologic and virologic parameters, progression from one clinical category to another (eg, from clinical category A to category B) may not

represent an indication to change therapy. For example, development of new OI, particularly in patients who have severe immunosuppression at the time therapy was initiated, may not reflect a failure of antiretroviral therapy but rather 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 numbers of available alternative antiretroviral agents. Although the efficacy of different combination antiretroviral regimens in children can likely be extrapolated from clinical trial data obtained for adults, data are limited concerning 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 previous 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 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, 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 to at least two new antiretroviral agents. Change in one drug or addi-

tion 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 to one containing PI agents, 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 such as whether they can be taken with food, other antiretrovirals, and other medications.
- When considering changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered.

Table 13 provides specific drug choices for changing a failing regimen. Because these issues are similar for all HIV-infected patients regardless of age, Table 13 is duplicated from the Guidelines for Use of Antiretroviral Therapy in HIV-Infected Adults and Adolescents.<sup>6</sup>

### MANAGING ADVERSE DRUG REACTIONS ASSOCIATED WITH THE TREATMENT OF PEDIATRIC HIV INFECTION

An adverse drug reaction is any response to a drug that is noxious, unintended, and occurs at doses normally used. The majority of available antiretroviral drug safety information for children are limited to monotherapy. The antiretroviral agents used for the treatment of HIV in children have all demonstrated individual and drug class toxicities that limit the doses and combinations that can be used safely.<sup>127</sup> The major toxicities associated with individual NRTI agents include hematologic cytopenias linked to ZDV; peripheral neuropathies linked to ddI, ddC, and d4T; and pancreatitis linked to ddI, ddC, d4T, and 3TC. With the exception of ZDV-induced anemia and neutropenia, most of these adverse drug reactions occur rarely in pediatrics. However, when pancreatitis and peripheral neuropathy do occur, they can be severe. The general principles of toxicity man-

**TABLE 13.** Suggested New Antiretroviral Regimens for HIV-infected Children Who Have Failed Antiretroviral Therapy<sup>a,b</sup>

Failed Previous Regimen	New Regimen (Not Listed in Priority Order)
2 NRTI agents + Nelfinavir	2 new NRTI agents + RTV; or IDV; or SQV + RTV; or NVP + RTV; or NVP + IDV <sup>c</sup>
2 NRTI agents + Ritonavir	SQV + RTV <sup>c</sup> or NFV + NVP
2 NRTI agents + Indinavir	SQV + RTV or NFV + NVP
2 NRTI agents + Saquinavir	NFV; or RTV; or RTV + SQV; or NVP + IDV
2 NRTI agents + Nevirapine	2 New NRTI agents + a PI
2 NRTI agents	2 New NRTI agents + a PI
1 NRTI	2 new NRTI agents + a PI
	2 New NRTI agents + Nevirapine

<sup>a</sup> These suggested alternative regimens have not been proven to be clinically effective.

<sup>b</sup> Considerations for changing antiretroviral therapy in HIV-infected adolescents should follow the *Guidelines for Use of Antiretroviral Agents in HIV-infected Adults and Adolescents*.<sup>6</sup>

<sup>c</sup> There are some clinical trials with surrogate marker data to support this recommendation.

agement are similar for adults and children. However, for many of the newer therapies (particularly PI agents), limited short-term and no long-term safety data or experience are available for infants, children, and adolescents. Thus, the information on which to base guidelines for management of children who experience toxicities in association with antiretroviral agents, especially when antiretroviral drugs are used in combination, is substantially more limited than that for adults. The data available from the PACTG 152 and PACTG 300 pediatric clinical trials indicate that combining some nucleoside analogues (ie, ZDV and ddI; ZDV and 3TC) does not substantially increase toxicity relative to monotherapy with the same agents.<sup>69,118</sup> Table 8 provides a detailed listing of the major toxicities and drug interactions associated with the antiretroviral agents currently available and other drugs commonly used in the management of HIV infection and its complications.

Although in general, antiretroviral drug toxicities are similar in children and adults, some toxicities occur at different frequencies and with different consequences in the two populations. For example, although the indirect hyperbilirubinemia associated with IDV usually is inconsequential for adults, the risk of kernicterus in neonates mandates routine monitoring of bilirubin levels in young infants treated with IDV, or who were born to women who were treated with IDV during late pregnancy. Additional examples of differing rates of toxicities experienced by adults and children include the occurrence of asymptomatic retinal depigmentation associated with ddI therapy in children, and the relative rarity of pancreatitis with ddI monotherapy in children compared with adults.

Another treatment issue that affects children differently from adults concerns the difficulty of successfully administering unpalatable formulations of antiretroviral agents to children. RTV solution, containing ~40% ethanol, is extremely bitter. NFV powder is insoluble and retains a gritty consistency even when suspended in liquid or semisolid food. Innovative techniques to increase palatability may be needed to enhance the acceptance of medications by children; various methods to increase the tolerability of RTV have been identified (Table 8).

Finally, certain measures important to minimize the risk of some toxicities may be difficult to implement in children. For example, IDV is associated with hematuria and nephrolithiasis secondary to crystallization of the drug in the urine; adequate hydration (ie, 48 ounces of fluid daily) is recommended to reduce the incidence of this side effect. However, it may be more difficult to ensure that voluntary fluid intake of this magnitude is achieved in children than in adults.

#### Principles of Management of Adverse Drug Reactions

1. Try to determine whether the adverse event is attributable to antiretroviral agents, to other medications, to progressive HIV infection itself, or to other infections that may complicate the course of HIV.

The clinical and laboratory manifestations of disease progression may mimic toxicities associated with some of the antiretroviral agents and other medications that the child is taking. Many HIV-infected children receive PCP prophylaxis with TMP/SMX concurrently with antiretroviral therapies. In such instances, the development of neutropenia may be attributable to TMP/SMX, to antiretroviral agents (eg, ZDV), or to HIV infection itself. Examples of infections that may cause signs and symptoms suggestive of drug toxicities include 1) *Mycobacterium avium* complex (MAC)<sup>128</sup>: bone marrow suppression, hepatic dysfunction, abdominal pain, and diarrhea; 2) cytomegalovirus (CMV)<sup>129</sup>: bone marrow suppression, hepatic dysfunction, bloody diarrhea, alteration in CNS; 3) Parvovirus<sup>130</sup>: anemia, rash; and 4) Epstein-Barr virus (EBV)<sup>131</sup>: hepatic dysfunction, bone marrow suppression, lymphadenopathy.

2. Continue therapy in the presence of nonlife-threatening toxicities.

Determination of the nature and severity of toxicity as well as the relative importance of each medication that the child is receiving is essential in developing a safe and effective treatment strategy. Table 14 depicts grades of severity of abnormal laboratory tests and adverse clinical events that may reflect common and potentially severe drug toxicities. As a rule, attempts should be made to continue antiretroviral therapy at effective doses except in the presence of severe (grade 4) or life-threatening toxicities, in which circumstances therapy should be stopped. Severe and possibly rapidly fatal complications including pancreatitis, hepatic failure, or severe skin rashes (with risk of progression to Stevens-Johnson syndrome) require discontinuation of the most suspect medication(s) and often at least temporary interruption of all medications possibly implicated. Lower-grade toxicities (grades 1 and 2) should prompt increased and more frequent observation, monitoring, and evaluation. Moderately severe toxicities (grades 2 and 3) may require consideration of specific interventions such as 1) the use of specific pharmacologic modulating therapies such as erythropoietin for the treatment of anemia<sup>132</sup> and granulocyte colony stimulating factor (G-CSF) for the treatment of neutropenia<sup>133</sup>; or 2) dose reduction of agents for which a range of effective dosages has been documented (eg, ZDV and ddI). Consultation with a clinician experienced in the care of HIV-infected children is recommended in these circumstances.

3. If there is a need to discontinue antiretroviral therapy for an extended period, many Working Group participants recommend stopping all antiretroviral agents simultaneously rather than continuing one or two agents alone. This is recommended in an attempt to minimize the risk of developing drug resistance in the face of potential increased viral replication.

Subtherapeutic drug levels and continued viral replication, as may be seen with intermittent use of antiretroviral drugs, is associated with in-

**TABLE 14.** Toxicity Levels Relevant to the Management of Adverse Drug Reactions (For Children >3 Months of Age)

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
<b>Hematology</b>				
Hemoglobin (g %)	10–10.9	7.0–9.9	<7	Cardiac failure secondary to anemia
Abs neutrophil count (cells/mm <sup>3</sup> )	750–1200	400–799	250–399	<250
Platelets (cells/mm <sup>3</sup> )	>75 000	50 000–75 000	25 000–49 999	<25 000 or bleeding
PT	1.0–1.25 × N <sup>b</sup>	1.26–1.5 × N	1.51–3.0 × N	>3 × N
PTT	1.1–1.66 × N	1.67–2.33 × N	2.34–3.0 × N	>3 × N
<b>Gastrointestinal</b>				
Bilirubin	1.1–1.9 × N	2.0 × 2.9 × N	3.0–7.5 × N	>7.5 × N
AST (SGOT)	1–4.9 × N	5.0–9.9 × N	10.0–15.0 × N	>15.0 × N
ALT (SGPT)	1.1–1.9 × N	5.0–9.9 × N	10.0–15.0 × N	>15.0 × N
GGT	1.1–4.9 × N	5.0 × 9.9 × N	10.0–15.0 × N	>15.0 × N
Pancreatic amylase	1.1–1.4 × N	1.5 × 1.9 × N	2.0–3.0 × N	>3.0 × N
Total amylase + lipase <sup>a</sup>	1.1–1.4 × N	1.5 × 2.4 × N	2.5–5.0 × N	>5.0 × N
Diarrhea	Soft stools	Liquid stools	Liquid stools and mild dehydration, bloody stools	Dehydration requiring IV therapy or hypotensive shock
Constipation	Mild	Moderate	Severe	Distention and vomiting
Nausea	Mild	Moderate, decreased oral intake	Severe, little oral intake	Unable to ingest food or fluid for >24 hours

<sup>a</sup> Both amylase and lipase must be elevated to the same grade or higher (ie, if total amylase is grade 4, but lipase is only grade 1, the toxicity grade is 1).

<sup>b</sup> N, normal.

creased risk of the development of genetic mutations associated with drug resistance. This has been shown to be especially true with PI agents. When toxicity considerations require interruption of treatment, it is preferable to discontinue all antiretroviral agents simultaneously. Likewise, during temporary disruptions of therapy, it is advisable to withhold all doses of the agent(s) throughout the period required to clarify and to ameliorate the problem rather than to sporadically withhold and administer individual doses. In circumstances where prolonged discontinuation of therapy is anticipated, it is recommended to change to a new agent(s) rather than to continue withholding one or more drugs. Finally, it is recommended that after resolution or improvement of the toxicity, all of the interrupted antiretroviral agents be simultaneously reinstated or a partially or completely new regimen be initiated.

### Common Adverse Drug Reactions

#### *Toxicities Associated With the Use of ZDV in the First 6 Weeks of Life*

Infants born to women with HIV infection who are treated during pregnancy are exposed to ZDV pre- and postnatally. Although it is not known precisely what role the neonatal component of the ZDV regimen plays in the reduction of vertical transmission, adherence to the neonatal component of PACTG 076 regimen seems prudent. Mothers who use the ZDV regimen have been reported to deliver infants with slightly lower hemoglobin levels (on average, 1 g lower) than those women who do not use ZDV. ZDV-associated anemia is most evident by 3 weeks of age. Although usually this is not problematic because the hemoglobin levels typically normalize by age 12 weeks, there have been occasional reports of clinically severe anemia in neonates perinatally ex-

posed to ZDV (at the age of the physiologic nadir of hemoglobin).

Special attention should be paid to the hemoglobin of the infant at birth, because this may help predict which infants will develop severe anemia during the course of their therapy. If clinically significant anemia (grades 3 or 4) develops within the first month of life (ie, within the first month of ZDV therapy), many experts recommend the use of transfusion or erythropoietin to sustain the use of ZDV until the issue of perinatal HIV infection has been clarified. However, if anemia does not become clinically severe until after the 4th week of ZDV therapy, ZDV could be discontinued at that time pending HIV virologic test results rather than subject the neonate to blood transfusion or erythropoietin.

Other potential ZDV-related toxicities such as neutropenia and liver function abnormalities seldom become evident in the first 6 weeks of life, and alternative explanations for these abnormalities should be sought before ZDV treatment is modified or discontinued.

In preclinical testing, ZDV yielded positive results on several in vitro and in vivo animal screening tests for carcinogenicity and mutagenicity. Prolonged, continuous exposure to high doses of ZDV administered to adult rodents has been associated with the development of noninvasive squamous epithelial vaginal tumors in 3% to 12% of females.<sup>134</sup> However, high concentrations of unmetabolized ZDV are excreted in the urine in mice, whereas in humans, ZDV is extensively metabolized and excreted in the urine as the glucuronide metabolite. In a study conducted by Glaxo–Wellcome, Inc, intravaginal infusions of saline containing high concentrations of ZDV (20 mg/mL) in mice resulted in the development of similar vaginal tumors, consistent with a possible topical effect of chronic local ZDV exposure of the vaginal

epithelium in mice, which also could occur secondary to reflux of urine containing highly concentrated ZDV from the bladder into the vagina.<sup>134</sup> No increase in the incidence of tumors in other organs has been reported from other studies of ZDV conducted in adult mice and rats. The risk of carcinogenicity with intrauterine ZDV exposure has been evaluated in two rodent studies that produced different results. In one study, daily administration of high doses (nearly the dose that is lethal for the rodent fetus and that is 25 to 50 times greater than the daily dose given to humans) to pregnant mice during the last third of gestation was associated with a statistically significant increase in lung, liver, and female reproductive organ tumors.<sup>135</sup> In a second study, pregnant mice were given one of several regimens of ZDV at dosages based on pharmacokinetic data in mice and humans that were intended to achieve blood levels somewhat higher (approximately threefold) than those achieved in clinical practice.<sup>136</sup> Some of the offspring also received ZDV for varying periods during their lives. No increase in the incidence of tumors was observed in the offspring, except in the subset that had been treated with ZDV postnatally; vaginal tumors occurred in this group.

The relevance of these animal data to humans is unknown. In the human data available to date from natural history studies and PACTG 076, no malignancies have been observed in short- and intermediate-term follow-up (up to 6 years of age) in 734 infants with in utero ZDV exposure.<sup>137</sup> Hypothetic risks must be balanced against the documented efficacy of perinatally administered ZDV in lowering rates of transmission of a lethal infection. A panel of specialists convened by NIH in January 1997 to review the animal carcinogenicity data concluded that the proven benefit of ZDV in reducing the risk of perinatal transmission outweighed the theoretic basis for concerns for transplacental carcinogenesis raised by the rodent studies. The panel also concluded that information regarding the theoretic risk of carcinogenesis should be discussed with all HIV-infected pregnant women in the course of counseling them about the benefits and potential risks of antiretroviral therapy during pregnancy.

#### *Anemia*

Anemia is one of the more common problems that develop in HIV-infected children receiving antiretroviral therapy. Among other causes the anemia may be ascribed to HIV infection itself or to antiretroviral therapy. Anemia is seen most commonly with ZDV treatment but may occur with other agents as well. In PACTG 152, 9.4% of children receiving ZDV developed anemia compared with 3.9% and 4.8% of children receiving ddI and ddI combined with ZDV, respectively.<sup>69</sup> In general, after the neonatal period and early infancy, children with anemia attributable to antiretroviral agents seldom require cessation of therapy and often respond to institution of erythropoietin if such is warranted because of excessive dependence on transfusions.<sup>132</sup>

#### *Neutropenia*

The problem of neutropenia in HIV-infected children receiving antiretroviral therapy is common. In PACTG 152, neutropenia was observed in 9.9% and 26.8% of children in the ZDV and ddI monotherapy arms, respectively.<sup>69</sup> In PACTG 300, the most common toxicity was neutropenia, occurring in 6.1% of patients.<sup>118</sup> In the experience of many pediatric HIV authorities, the definition of clinically significantly severe neutropenia in the HIV-infected child differs markedly from the criteria that applies to an otherwise healthy child or to a child with a hematologic malignancy. HIV-infected infants and children appear to tolerate lower absolute neutrophil counts with infrequent but not absent complications. Mild to moderate neutropenia (grades 1, 2, and 3, absolute neutrophil count  $>250$  cells/mm<sup>3</sup> in children older than 3 months) (Table 14) in the absence of associated signs or symptoms that warrant concern, such as persistent fever or focal or generalized infection, generally is not an indication for immediate reduction or cessation of therapy. Few children with HIV suffer infectious complications of neutropenia unless it is quite severe and prolonged (grade 4, absolute neutrophil count  $<250$  cells/mm<sup>3</sup>). In some children, neutropenia represents a manifestation of their HIV disease and may improve with enhanced suppression of HIV replication resulting from a change in their antiretroviral regimen. In other cases, it may be attributable to bone marrow suppression secondary to a nonantiretroviral drug toxicity. If the patient is clinically stable but significant absolute neutropenia persists, supportive therapy such as G-CSF should be initiated before modifying the antiretroviral regimen.<sup>133</sup> If a child develops neutropenia while on an antiretroviral regimen containing ZDV, that agent should be considered the most likely cause. After confirmation that the neutropenia is persistent rather than transient, evaluation for other etiologies should be initiated and consideration given to instituting G-CSF therapy. If neutropenia does not improve within 1 week of instituting G-CSF, the dose can be increased. When no alternative etiology is identified and the response to G-CSF is not adequate, consideration should be given to interrupting antiretroviral agents including ZDV, but for as brief a period as possible.

#### *Thrombocytopenia*

Thrombocytopenia (ie, platelet count  $<100\,000$  cell/mm<sup>3</sup>) in children with HIV infection, like neutropenia, is relatively common.<sup>138</sup> Although thrombocytopenia may occur in conjunction with antiretroviral therapy, it also occurs in 30% of untreated children with HIV infection. Severe thrombocytopenia occurred in 2% of children receiving ddI, ZDV/ddI, or ZDV/3TC therapy in PACTG 300, but was present at entry into study in 2.2% of enrollees. Children with undiagnosed and untreated HIV infection initially may present with thrombocytopenia as the first manifestation of disease that precipitates seeking medical attention. This, in fact, appears to be much more common than the development of throm-

bocytopenia secondary to antiretroviral therapy.<sup>139,140</sup> Thrombocytopenia may resolve once antiretroviral therapy is initiated. When thrombocytopenia is severe (<20 000 cells/mm<sup>3</sup>), treatment with intravenous immunoglobulin (IVIG) is indicated (1 g/kg per day for 2–3 consecutive days). If this fails, a course of corticosteroids may avail.

#### Pancreatitis

Pancreatitis has been related to treatment with most antiretroviral agents in children, particularly with ddI, but is relatively uncommon.<sup>70,141</sup> Other agents used for treatment or prophylaxis of OI, such as pentamidine and isoniazid, have a much greater propensity to cause pancreatitis than do antiretroviral drugs. Several infections that occur at increased frequencies in children with HIV infection also may cause pancreatitis. Unfortunately, laboratory measurement of total amylase has not been a good indicator of clinical pancreatitis and thus is not an effective screening tool.<sup>142</sup> In PACTG 152, nearly 8% of studied subjects had elevated amylase, but few had clinical pancreatitis.<sup>69</sup> In PACTG 300, severe pancreatitis developed in only 1.2% of patients on therapy, and elevated amylase and lipase occurred in only 1 subject. The risk of pancreatitis in combination regimens that include PI agents remains to be determined. As in adults, much of the elevation of amylase in children with HIV infection is related to salivary gland involvement.<sup>143</sup> Before making any adjustment of therapies based on elevated amylase as chemical evidence of pancreatic dysfunction, either lipase or fractionated amylase should be performed to determine pancreatic or salivary origin of the elevated amylase. If clinical pancreatitis develops, the agent most likely to be causally related should be stopped.

#### Hepatitis

Although the toxicity profiles of many antiretroviral agents include elevated transaminases, the task of identifying the cause(s) of abnormal liver function tests in a given patient can be complicated. In addition to drug toxicity, the differential diagnosis includes HIV-induced hepatitis or hepatitis caused by another infectious agent such as MAC, hepatitis B, hepatitis C, EBV, or CMV. The diagnostic considerations and evaluation should reflect an individual patient's current medications, HIV viral load, and immune function, as well as the relevant medical history. Before making any changes in antiretroviral therapies because of elevated transaminases, the several possible explanations need to be considered and evaluated thoroughly. Other nonantiretroviral drugs (eg, fluconazole) may more likely contribute to hepatotoxicity and should be discontinued before stopping antiretroviral therapy. If an adverse drug reaction is the most likely explanation for a severe hepatic toxicity (grade 3 or 4) (Tables 14, 15), the suspect drug should be discontinued temporarily and carefully reintroduced when transaminase levels decrease only if the offending drug is essential for patient management.

**TABLE 15.** Drug Combinations with Potential for Additive Toxicity

Bone marrow suppression	<u>ZDV</u> , <u>TMP/SMX</u> , <u>ganciclovir</u> , <u>interferon-<math>\alpha</math></u> , amphotericin B, carbamazepine, dapsone, didanosine, foscarnet, lamivudine, pentamidine, phenytoin, rifabutin, zalcitabine, fluconazole
Hepatotoxicity	<u>Rifabutin</u> , <u>INH</u> , carbamazepine, fluconazole, itraconazole, ketoconazole, rifampin, TMP/SMX, lamivudine, stavudine, zalcitabine, ZDV, nevirapine, ritonavir
Peripheral neuropathy	<u>Stavudine</u> , <u>ganciclovir</u> , <u>zalcitabine</u> , dapsone, didanosine, fluconazole, foscarnet, INH, phenytoin, ritonavir
Nephrotoxicity	<u>Ganciclovir</u> , <u>foscarnet</u> , <u>amphotericin b</u> , <u>aminoglycosides</u> , acyclovir, pentamidine, indinavir (nephrolithiasis)
Pancreatitis	<u>Pentamidine</u> , <u>stavudine</u> , <u>zalcitabine</u> , <u>didanosine</u> , fluconazole, lamivudine, PI agents
Skin toxicities (vasculitis/allergy)	<u>Nevirapine/delavirdine</u> , <u>TMP/SMX</u> , <u>nelfinavir</u> , dapsone, indinavir, stavudine, lamivudine, phenytoin, filgrastim, saquinavir (photo-sensitivity)
Gastrointestinal	<u>Atovaquone</u> , <u>didanosine</u> , <u>ritonavir</u> , indinavir, nelfinavir, saquinavir, lamivudine, stavudine, delavirdine, nevirapine, foscarnet, azithromycin, clarithromycin, ganciclovir, fluconazole, rifabutin
Cardiotoxicities	<u>Astemizole</u> , <u>terfenadine</u> , <u>cisapride</u> , <u>triazolam</u> , <u>midazolam with macrolides</u> , <u>azoles</u> or <u>PI agents</u> ; methadone, phenytoin, pentamidine, zalcitabine
Myopathy/myositis	<u>ZDV</u> , <u>atovaquone</u> , acyclovir, ganciclovir, rifabutin
Constitutional symptoms (headaches, fatigue, malaise, nausea)	Indinavir, nelfinavir, ritonavir, saquinavir, stavudine, lamivudine, zalcitabine, delavirdine, nevirapine, atovaquone, acyclovir, foscarnet, epoetin alfa

Underlined drugs used in combinations are most likely to cause adverse reactions.

#### Drug Interactions Involving Agents Used in the Management of HIV Infection

Appropriate management of HIV-infected children frequently involves the use of multiple drug regimens that place these children at high risk for drug interactions. Children with advanced HIV disease frequently receive more than 15 different medications, some of which are investigational and many associated with limited published experience in children.<sup>144</sup> Lack of information about drug interactions of newly approved antiretroviral agents and other medications makes it difficult to predict the likelihood and consequences of these interactions.

Types of drug interactions include additive toxicity and pharmacokinetic interactions. In general, drug interactions that alter the pharmacologic effects can increase or decrease serum levels of drugs by changing absorption, distribution, metabolism, or elimination. The risk of such drug interactions increases with the number of medications taken, the use of experimental or new drugs, and when drugs used in combination share similar pharmacodynamics or toxicities. In combination regimens, drug interactions can result in effects that are additive, synergistic, or antagonistic. Table 8 provides detailed information on the most common known drug interactions of many of the medications used commonly in pediatric HIV disease.

Table 15 provides a list of medications that share toxicities, thus enhancing the potential for adverse drug interactions.

Several classes of medications often prescribed for adolescents, notably oral contraceptives and antidepressants/anxiolytics, have important interactions with antiretroviral drugs. In the case of contraceptives, RTV and NFV decrease estradiol levels, potentially reducing their efficacy. Clinicians may consider switching to progestin-only formulations of oral or injectable contraceptives. NVP may have the same effect on estradiol levels, although there is less information about this medication interaction. IDV modestly increases Ortho Novum levels, but no dosage or medication changes are recommended. With respect to psychotropics, RTV should not be used with the antidepressant bupropion and many benzodiazepines (anxiolytics). RTV also significantly increases levels of the antidepressant desipramine (and other tricyclics) and fluoxetine (serotonin reuptake inhibitor). If these agents are used concomitantly, toxicity should be anticipated and close monitoring is essential. IDV may have the same effects, although there is less information available.

Clinicians should be aware of the following serious, potentially life-threatening drug interactions when taking care of HIV-infected patients: 1) the use of astemizole/terfenadine, cisapride, triazolam, or midazolam in combination with macrolides, azoles, or PI agents may result in cardiac arrhythmias; 2) the use of foscarnet in combination with pentamidine may result in hypocalcemia; 3) the use of ganciclovir in combination with aminoglycosides or amphotericin B may result in renal failure; 4) the use of ganciclovir in combination with imipenem-cilastatin may result in seizures; 5) the use of ddC or ddI in combination with pentamidine increases the risk for life-threatening pancreatitis; and 6) PI agents should not be used with meperidine (Demerol) and propoxyphene (Darvon), and concurrent administration with alfen-

tanil (Alfenta), fentanyl (Sublimaze), and methadone results in increased levels of these narcotics, which can depress respiration. All of the above drug combinations should be avoided.

## MANAGING COMPLICATIONS OF HIV INFECTION

### Infectious Complications

As a group, the infectious complications of HIV infection comprise the most frequent AIDS-defining conditions in children with AIDS in the United States. These include opportunistic protozoan, fungal, and viral infections as well as recurrent episodes of bacterial infection of varying severity. In 1996, 678 cases of AIDS were reported in US infants and children younger than age 13, with 578 AIDS-indicator OI reported in these children. Pneumonia caused by *P carinii*, esophageal candidiasis, and recurrent serious bacterial infections alone accounted for 70% of OI and 43% of all AIDS-indicator conditions. By comparison, the most common noninfectious AIDS-indicator conditions reported in 1996 were lymphoid interstitial pneumonia (or pulmonary lymphoid hyperplasia), which occurred in 20% of newly reported cases of AIDS in children, HIV encephalopathy in 17%, and HIV wasting syndrome in 15% of cases. Relative frequencies of individual infections and noninfectious AIDS-indicator conditions observed in 1996 data were similar to those in previous years (Table 16).<sup>145,146</sup>

### Considerations Regarding the Prevention of Secondary Infections

A comprehensive approach to the prevention of opportunistic and recurrent serious bacterial infections in HIV-infected children requires both systematic monitoring of immunologic and virologic status and the administration of immunizations and prophylactic antimicrobials, and the selective use of immunoglobulin replacement therapy. Defining optimal guidelines for preventive treatment (whom to

**TABLE 16.** AIDS-indicator Conditions Reported in US Infants and Children <13 Years of Age With AIDS, 1995 and 1996

	1995 N = 800		1996 N = 678	
PCP	212	27%	162	24%
LIP	147	19%	141	20%
HIV wasting syndrome	146	18%	100	15%
HIV encephalopathy	132	17%	114	17%
Candidiasis of esophagus	125	16%	87	13%
Bacterial infections, multiple or recurrent	123	15%	158	23%
<i>M avium</i> or <i>M kansasii</i> , disseminated	50	6%	41	6%
CMV disease other than retinitis	48	6%	37	5%
HSV	46	6%	31	5%
Cryptosporidiosis	27	3%	20	3%
Candidiasis of bronchi, trachea, or lungs	18	2%	20	3%
Malignancies	13	2%	10	1.5%
Mycobacterial disease, disseminated	11	1%	7	1%
Toxoplasmosis of brain	9	1%	2	0.3%
CMV retinitis	8	1%	10	1.5%
Cryptococcosis	7	1%	1	0.2%
Progressive multifocal leukoencephalopathy	4	0.5%	1	0.2%
<i>M tuberculosis</i> , disseminated	2	0.3%	1	0.2%
Coccidioidomycosis, disseminated	0	0%	1	0.2%
Isosporiasis and histoplasmosis	0	0%	0	0%

This table is modified from references 145 and 146.

treat, when to start, what to use) is a challenging task, given the vast array of opportunistic pathogens, the limited number of available effective prophylactic agents, and the need to balance the risk of incurring infection against the expense, inconvenience, and potential for developing toxicity, resistance, and drug interactions inherent in preventive therapies. Acute episodes of infection may be life-threatening. For those conditions in which a given preventive treatment has been shown safe and effective, primary prophylaxis can reduce the likelihood of occurrence of certain OI. In contrast to recurrent serious bacterial infections, few of the protozoan, fungal, or viral infections complicating HIV are curable with currently available treatments. For many of these conditions, after the initial infectious episode, secondary prophylaxis in the form of lifelong suppressive therapy is indicated to prevent recurrent clinical diseases.

Guidelines for the prevention of OI in both children and adults infected with HIV have been developed jointly by the USPHS and the IDSA and were published recently.<sup>10</sup> These guidelines are republished as a companion document in this supplement to which readers are referred for guidance on preventing OI in children with HIV infection. (See the "Pediatric Note" sections included in the discussion of each opportunistic organism, as well as the pediatric-specific tables and figure.) In general, adolescents with HIV infection should be managed according to the guidelines for prevention of OI in adults.

The remainder of this article addresses the treatment of specific infectious and noninfectious complications of HIV infection in children, as well as additional important management issues respecting pediatric HIV/AIDS.

### Treatment of Specific Secondary Infections

#### PCP

##### Incidence

Of 6891 children reported with perinatal AIDS cases through 1996, 34.1% have had PCP as a presenting AIDS-indicator condition.<sup>146</sup> Through 1995, the incidence of PCP by 1 year of age in infants with HIV infection was 12%.<sup>147</sup>

##### Diagnosis

Bronchoalveolar lavage (BAL) (usually preferred), tracheal aspirate, or induced sputum should be evaluated for the presence of *P carinii* cysts and/or trophozoites with the methenamine silver nitrate, Giemsa, toluidine blue, or fluorescent monoclonal antibody stain methods or by histopathologic evaluation of biopsied lung tissue (most sensitive method).<sup>148</sup>

##### Treatment

Trimethoprim/sulfamethoxazole (TMP/SMX) is the treatment of choice for PCP (20/100 mg/kg per day, intravenously, in 4 divided doses). The usual course of treatment is 21 days. For patients intolerant of TMP/SMX, intravenous pentamidine is recommended (4 mg/kg per day in a single daily infusion).

Based on studies in adults, a short course of corticosteroids may be indicated in some cases of PCP of

moderate or great severity. Indications for corticosteroid include a  $Pao_2$  value of <70 mm Hg or an alveolar-arterial gradient of >35 mm Hg. An initial dose of 2 mg/kg per day of prednisone (or equivalent doses of other corticosteroids), in 4 divided doses, is recommended.<sup>149</sup>

#### Toxoplasmosis

##### Incidence

Infection of the CNS with *Toxoplasma gondii* is uncommon in HIV-infected children, being reported as an AIDS-indicator condition in 0.3% of newly reported cases of pediatric AIDS in 1996.<sup>146</sup>

##### Diagnosis

A presumptive diagnosis of CNS toxoplasmosis is based on serologic evidence of infection and the presence of a space occupying lesion on imaging studies of the brain. Definitive diagnosis, based on brain biopsy, is indicated for patients who fail to respond to empiric therapy.<sup>150</sup>

Congenital toxoplasmosis is diagnosed by the demonstration of specific IgM or IgA serum antibody to *Toxoplasma*. HIV-infected women are at increased risk of transmitting *Toxoplasma* to their fetuses,<sup>151</sup> and serologic testing for *Toxoplasma* should be performed on all HIV-infected pregnant women. A pregnant woman with symptomatic *Toxoplasma* infection should be treated. Infants whose mothers are both HIV-infected and seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis. If a woman has a symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be considered, regardless of whether the mother was treated during pregnancy.<sup>152</sup>

In the United States, routine serologic screening of HIV-infected children for *Toxoplasma* infection is not recommended. However, in regions with a high incidence of *Toxoplasma* infection, serologic testing may be performed on HIV-infected children after 12 months of age. For children receiving PCP prophylaxis with a medication other than TMP/SMX, serologic testing for *Toxoplasma* infection may be considered to identify those who require additional prophylaxis against *Toxoplasma*. As in adults, adolescents not already known to be infected with *Toxoplasma* should undergo serologic testing.

##### Treatment

In the child with HIV infection, treatment of symptomatic toxoplasmosis is followed without interruption by lifelong suppressive treatment. The therapy of choice is sulfadiazine (85–120 mg/kg per day in 2–4 divided doses), pyrimethamine (1 mg/kg per day or 15 mg/m<sup>2</sup> per day as a single oral dose, maximum dose 25 mg), and folinic acid (5–10 mg every 3 days). An alternative regime is clindamycin (20–30 mg/kg per day in 4 divided doses), pyrimethamine, and folinic acid.

##### Prevention of Recurrence

Lifelong suppression is indicated after treatment for *Toxoplasma* encephalitis. The recommended therapy is sulfadiazine, pyrimethamine, and folinic acid

in the same doses as for treatment. This regimen also provides effective prophylaxis against PCP. An alternative regimen is clindamycin, pyrimethamine, and folinic acid; however, this does not provide effective PCP prophylaxis.

### *Cryptosporidiosis*

#### *Incidence*

Cryptosporidiosis has been reported in 3% to 4% of children followed in some US pediatric HIV centers, but it may occur more frequently outside of the United States.<sup>153,154</sup> Outbreaks have been associated with ingestion of contaminated drinking water in large metropolitan areas. The parasite is transmitted by ingestion of oocysts excreted in the feces of infected animals and humans. Person-to-person transmission is common in day care centers. Several outbreaks have been associated with public swimming pools.

#### *Diagnosis*

Concentrated stool samples should be evaluated with a modified acid fast procedure. Diagnosis also can be made on small intestinal biopsy. At least three stool samples should be submitted for oocyst evaluation.<sup>155</sup>

#### *Treatment*

Supportive care with hydration and nutritional supplementation is recommended. There is no proven effective therapy in patients with AIDS. Numerous agents including paromomycin, azithromycin, octreotide, oral hyperimmune bovine colostrum, and oral IVIG have been reported to have benefit. Despite the availability of these and other evolving modalities, there are little data supporting the use of any therapies. The recommended therapeutic agent of choice is paromomycin (30–40 mg/kg per day in 3–4 divided doses, maximum 1000 mg/day), based on limited efficacy data.<sup>156–158</sup> Newer agents currently under investigation include roxithromycin and nitazoxanide.

### *TB*

#### *Incidence*

Incident case rates of TB (ie, tuberculous disease, not merely infection) in HIV-exposed or -infected children are reported to be 10- to 100-fold higher than those in children of comparable age in the general US population.<sup>159</sup> Multiply resistant strains of *Mycobacterium tuberculosis* appear to be common in children with HIV infection and TB or in the adults infected with TB to whom they are exposed (15%–20%).<sup>159</sup> *M tuberculosis* can cause extrapulmonary or disseminated disease in HIV-infected children.

Because children with HIV infection are considered at high risk for TB, annual tuberculin skin testing of this population is recommended, beginning at 9 to 12 months of age using intradermally injected 5 TU PPD. A  $\geq 5$  mm of induration is considered to be a positive (diagnostic) reaction in individuals with HIV infection. Multiple puncture TB skin tests (eg, Tine) are not recommended. The use of control skin test antigens at the time of PPD testing to identify anergy is of uncertain value and no longer routinely

recommended; however, mumps and *Candida* are the appropriate control antigens if anergy testing is performed.<sup>160</sup>

#### *Diagnosis*

Diagnosis of TB disease in HIV-infected children is complicated by the frequent presence of preexisting or coincidental fever, pulmonary symptoms, and radiographic abnormalities. A definitive diagnosis of pulmonary TB requires isolation of *M tuberculosis* from expectorated sputum, BAL fluid, (early morning) aspirated gastric fluid, or biopsied lung tissue. Strenuous efforts should be made to obtain these diagnostic specimens (three each of sputum and gastric aspirate specimens) whenever a presumptive diagnosis of TB is made or if it is highly suspected despite negative skin testing results (ie, because of a history of exposure to another individual with active TB). Smears of specimens should be prepared, stained (using either the Ziehl–Neelsen method or auramine–rhodamine staining in conjunction with fluorescence microscopy) and evaluated for the presence of acid-fast organisms. Specimens should be cultured; isolation of *M tuberculosis* may take up to 10 weeks but may be hastened by DNA probes. Susceptibility testing should be performed on all isolates.

#### *Treatment*

Initial empiric treatment of active disease in HIV-infected children should consist of a four-drug regimen that include isoniazid (10–20 mg/kg per day in 1–2 oral doses, maximum 300 mg/day); rifampin (10–20 mg/kg per day in 1–2 oral doses, maximum 600 mg/day); pyrazinamide (30 mg/kg per day in 1–2 oral doses); and either streptomycin (20–30 mg/kg per day intramuscularly divided q12h) or ethambutol (15 mg/kg per day in single oral dose).<sup>161</sup> Subsequent modifications of therapy should be based on susceptibility testing if possible. Directly observed therapy is strongly recommended. A tablet formulation combining isoniazid, rifampin, and pyrazinamide is available, although pediatric use has not been evaluated and the fixed doses would not be appropriate for many children. For HIV-infected children with active disease, the minimum recommended duration of antituberculous drug treatment is 6 to 12 months; for children with extrapulmonary disease involving the bones or joints, CNS, or miliary disease, the minimum recommended duration of treatment is 12 months.<sup>162,163</sup> These recommendations assume that the organism is susceptible to the medications, that compliance with the medications has been ensured, and that the child has had a clinical and microbiologic response to therapy.

### *Disseminated Infection With MAC*

#### *Incidence*

Disseminated infection with *M avium* complex (MAC) rarely occurs during the first year of life; its frequency increases with age and declining CD4+ count, and it is a frequent complication of advanced immunologic deterioration in HIV-infected adults and children.<sup>164</sup> Estimates of disseminated MAC prevalence in advanced HIV disease range from 30% to 50%. Disseminated disease in adults and in chil-

dren older than 6 years occurs when CD4+ counts fall below 50/ $\mu$ L.<sup>165</sup> In children younger than 2 years, MAC occurs at substantially higher CD4 counts, accounting for the recommended age-variable, CD4+ count-based thresholds for initiating prophylaxis for MAC in children.<sup>10,166</sup> Clinical features of disseminated MAC infection include fevers, night sweats, neutropenia, anemia, weight loss or failure to thrive, abdominal pain, and diarrhea.<sup>167</sup>

#### Diagnosis

Diagnosis of MAC is accomplished by isolation of the organism from the blood or from biopsied specimens of bone marrow, lymph node, or other tissues. Identification of MAC in stool or respiratory tract secretions indicates colonization but not necessarily disease. Recovery of organisms from blood is enhanced by use of a radiometric broth medium culture technique.<sup>168</sup> Although currently not widely available, the use of DNA PCR may be of value for diagnostic purposes in the future.<sup>169</sup>

#### Treatment

Combination therapy with at least two drugs is recommended. Clarithromycin (15 mg/kg per day divided in 2 oral doses, maximum 500 mg) and ethambutol (15–20 mg/kg per day in a single oral dose, maximum 1600 mg) should be included,<sup>170</sup> with the possible addition of rifabutin (5–10 mg/kg per day once daily, maximum 300 mg) or ciprofloxacin (20–30 mg/kg per day intravenously or orally once a day, maximum 1.5 g) or azithromycin (10 mg/kg once daily). Susceptibility testing may be helpful in directing the choice of agents when resistance is suspected. Regular ophthalmologic monitoring for potential drug-associated optic neuritis is recommended for patients receiving ethambutol.

For secondary prevention of recurrent disease, lifelong prophylaxis with clarithromycin is recommended (15 mg/kg/day in 2 divided doses, maximum 500 mg), in combination with at least one of the following: ethambutol (15–20 mg/kg per day once daily), rifabutin (5 mg/kg per day once daily, maximum 300 mg), ciprofloxacin (20–30 mg/kg per day in 2 divided doses, maximum 1.5 g), or azithromycin (5 mg/kg once daily, maximum 250 mg, or 20 mg/kg once weekly).

### Invasive Bacterial Infections

#### Incidence

Of cases of pediatric AIDS reported in 1996, 20% presented with recurrent serious bacterial infections as an AIDS-defining condition.<sup>146</sup> Pneumococcus is the most common invasive bacterial pathogen in children with HIV infection, accounting for 25% to 50% of episodes.<sup>171,172</sup>

#### Diagnosis

Isolation of a pathogenic bacterial organism from a normally sterile site or, on occasion, the detection of bacterial antigens establishes the diagnosis.

#### Prophylaxis

All HIV-infected children should be vaccinated with the conjugate *Haemophilus influenzae* type b vaccine in infancy and with the 23-valent polysaccharide pneumococcal vaccine at 24 months of age.<sup>10</sup> Revac-

ination with the pneumococcal vaccine is recommended after 3 to 5 years for children age 10 and younger and after 5 years for children older than age 10.

### Hypogammaglobulinemia or Recurrent Bacterial Infections

Daily TMP/SMX (150/750 mg/m<sup>2</sup>/day in 2 divided oral doses daily) may be useful in the prevention of recurrent bacterial infections, including recurrent *Salmonella* infections, and is recommended by some authorities for patients with frequent and severe recurrent invasive bacterial infections.<sup>10</sup> TMP/SMX prophylaxis cannot be expected to prevent all pneumococcal (or other bacterial infections), because the majority of penicillin-resistant strains also are resistant to TMP/SMX. Other antibiotics may be considered for prophylaxis in individual cases, recognizing the risk of development of drug-resistant organisms. IVIG (400 mg/kg per month) may be given if there are recurrent infections despite TMP/SMX prophylaxis, noting that IVIG may not add additional benefit to children receiving daily TMP/SMX.<sup>171,172</sup>

#### Indications for IVIG Therapy

1. Significant recurrent bacterial infections despite a trial of appropriate antimicrobial prophylaxis in infants and children with HIV infection who have humoral immune defects (hypo- or hypergammaglobulinemia). Some authorities recommend initiating IVIG therapy without first attempting chemoprophylaxis;
2. Absence of detectable antibody to measles in children who have received two measles immunizations and who live in regions with a high prevalence of measles;
3. HIV-associated thrombocytopenia (platelet count <20 000) despite antiretroviral therapy (IVIG dose, 1 g/kg given daily for two to three consecutive days); and
4. Chronic bronchiectasis in children with HIV infection that is suboptimally responsive to antimicrobial and pulmonary therapy may improve with high-dose IVIG (600 mg/kg per month).

#### Treatment

Therapy of bacterial infections should be based on antibiotic susceptibility. The local prevalence of *Streptococcus pneumoniae* with reduced susceptibility to penicillin and other candidate antimicrobials should be considered when selecting the initial empiric therapy.<sup>173</sup>

### Persistent or Recurrent Mucocutaneous Candidiasis

#### Incidence

*Candida* is found on all skin and mucosal surfaces. Oral candidiasis is the most common oral complication associated with HIV infection in children,<sup>174</sup> with a wide-ranging reported overall prevalence of 11% to 72%. Among asymptomatic children, the reported prevalence is 11% to 20%.<sup>175</sup> The frequency of *Candida* esophagitis is not well defined because of institutional differences in the use of endoscopy for diagnosis.

### Prevention

Primary prophylaxis is not indicated; however, good oral hygiene and daily oral debridement may be helpful. For all infants and children, this includes wiping the gums, tongue, and palate with a moistened wash cloth 2 times daily. Rinsing with water after eating and drinking may be helpful. Secondary prophylaxis may be indicated if candidiasis recurs frequently or becomes persistent. Lifelong prophylaxis with an azole should be considered in cases of recurrent *Candida* esophagitis, using fluconazole (3–6 mg/kg per day in 1–2 divided doses) or ketoconazole (5–10 mg/kg in 1–2 doses). Long-term use of azoles should be limited because of the risk of developing resistant organisms. Other options recommended by some specialists include topical treatment with nystatin, gentian violet, or oral amphotericin B suspension (1.0 mL per dose for all age groups).<sup>176</sup>

### Diagnosis

There are four types of oral lesions: pseudomembranous (thrush), erythematous (atrophic), hyperplastic, and angular cheilitis. Confirmation of a clinically suspected diagnosis can be made by observing blastospores or pseudohyphae on a KOH-stained specimen or by isolation of *Candida* in culture. *Candida* esophagitis is diagnosed by clinical symptoms, endoscopy, and biopsy; barium swallow is not a reliable means of establishing or excluding the diagnosis.

### Treatment

Topically applied nystatin (as a suspension, cream, or tablets at a dose of 100 000–500 000 U 4 times per day), amphotericin B, clotrimazole troches (3–5 per day), and intraoral use of vaginal azole cremes or suppositories are appropriate first-line therapy for oral candidiasis. Topical amphotericin (1 mL for all ages) is administered orally by medicine dropper swished, retained briefly, then swallowed. For infants and young children, clotrimazole troches may be placed in a clean nipple in which additional holes have been punctured. The plunger from a 20 mL syringe should be placed on the distal end of the nipple ring to prevent the swallowing of too much air. Azoles such as fluconazole (3–6 mg/kg per day in 1–2 orally administered doses) and ketoconazole (5–10 mg/kg in 1–2 doses) for 5 days are appropriate second-line therapies. However, some patients may need longer or repeated courses of therapy.

Treatment of *Candida* esophagitis is based on severity of symptoms, current medications taken, compliance, presence or absence of neutropenia, and concomitant infections. Many patients can be treated orally with fluconazole (3–6 mg/kg once daily, maximum 200 mg). In patients with severe disease or who are refractory to oral treatment, intravenous amphotericin B is indicated<sup>177</sup> (0.5–1.0 mg/kg per day).

### *Cryptococcus neoformans*

#### Incidence

*Cryptococcus neoformans* is a ubiquitous fungus present in the soil and in bird droppings. Between

5% and 10% of HIV-infected adults acquire this infection. It is seen less frequently in children, reported as a pediatric AIDS-indicator condition in 0.1% of cases in 1996.<sup>146</sup> Meningitis is the most common extrapulmonary manifestation.<sup>178</sup> Fever, headache, and altered mental status are the most common presenting signs.

#### Diagnosis

Examination of the CSF for cryptococcal antigen and yeast forms with an India ink preparation and culturing CSF are indicated when this infection is suspected. The organism usually appears as an encapsulated budding yeast. In some cases in which a lumbar puncture is not possible, a negative test result for serum cryptococcal antigen may help rule out cryptococcal meningitis. Routine screening for serum cryptococcal antigen is not recommended.

#### Treatment

Treatment should be initiated with amphotericin B (0.5–1.0 mg/kg, iv, once daily), with or without flucytosine (50–150 mg/kg per day in 4 divided oral doses, monitoring drug concentrations), for 14 days and/or until there is appropriate clinical improvement. Thereafter therapy can be changed to orally administered fluconazole (6–12 mg/kg per day, maximum 400 mg) or itraconazole (2–5 mg/kg per day in 1–2 divided doses, maximum 400 mg) to complete an 8- to 10-week course.<sup>179</sup>

#### Prevention of Recurrence

After therapy, secondary prophylaxis with fluconazole (3–6 mg/kg per day, maximum 200 mg) may be effective. Alternatives include itraconazole (2–5 mg/kg per day in 1–2 divided doses) or amphotericin B (0.5–0.7 mg/kg per day, iv, 1–3 times per week).<sup>179</sup>

### CMV

#### Incidence

Infection with human CMV is common and usually inapparent. The seroprevalence in immunocompetent adults in developed countries ranges from 40% to 80%. In ~1% of cases of pediatric AIDS reported in 1996, CMV infection was an AIDS-indicator condition.<sup>146</sup> Transmission occurs both horizontally by contact with virus-containing saliva, sexual fluids, or urine, and vertically from infected women to their offspring. More than 90% of HIV-infected pregnant women are CMV-infected. The risk of both congenital and perinatal acquisition of CMV is increased in infants born to women infected with both CMV and HIV. CMV may be associated with accelerated progression of HIV disease in the dually infected infant.<sup>129</sup> Retinitis, CNS infections, and infection of the gastrointestinal tract are important manifestations of CMV infection in late stages of HIV infection.

#### Diagnosis

Recovery of virus from tissues (eg, endoscopically guided biopsies of gastrointestinal or pulmonary tissue) may provide evidence of disease in symptomatic patients. Serologic testing of children older than 1 year of age identifies infection reliably but does not

distinguish dependably between active and resolved disease.

Some authorities recommend testing all infants with HIV infection for CMV infection with a urine culture in the first several months of life to identify infants with congenital, perinatal, or early postnatal infection. In addition, annual CMV antibody testing of previously seronegative (and culture-negative) infants and severely immunosuppressed children, beginning at 1 year of age, will identify those who develop occult CMV infections, thus permitting appropriate screening for retinitis.<sup>129</sup>

The funduscopic appearance of CMV retinitis is distinctive. Children with HIV infection who are CMV-infected should have a dilated retinal examination performed by an ophthalmologist experienced in this diagnosis every 4 to 6 months once they are severely immunocompromised (immune category 3). Older children and adolescents should be counseled to report "floaters" and visual changes.

#### *Therapy*

Ganciclovir (10 mg/kg per day in 2 divided doses, iv, over 1–2 hours for 14–21 days, followed by lifelong maintenance therapy with 5 mg/kg per day, iv, 5 days per week) or foscarnet (180 mg/kg per day in 3 divided doses, iv, over 1–2 hours for 14–21 days followed by lifelong maintenance therapy with 90–120 mg/kg per day, iv, as a single daily dose) are the treatments of choice. Foscarnet has been associated with increased length of survival relative to ganciclovir in adult patients. Doses of both drugs should be modified in patients with renal insufficiency. Combination therapy with ganciclovir and foscarnet has been shown to delay progression of retinitis in some patients failing monotherapy.<sup>180,181</sup> Intraocular ganciclovir implants have been shown to be effective in delaying progression of ipsilateral retinitis in several studies, but they do not prevent extension to the contralateral eye or development of systemic infection.<sup>182,183</sup> Intraocular injection of ganciclovir is an additional treatment option for retinitis, but current data are limited.<sup>184</sup> Cidofovir is effective in treating CMV retinitis in adult patients who are intolerant of other therapies, but nephrotoxicity may occur. The pharmacokinetics of intravenous cidofovir are currently being studied in children.

### *HSV*

#### *Incidence*

HSV infections are relatively infrequent in neonates, but occur with increasing frequency throughout childhood and in adults, with incidence rates that vary inversely with socioeconomic status. They may represent either a primary or recurrent infection and are caused by HSV types 1 and 2.<sup>185</sup> In 1996, 5% of new cases of pediatric AIDS were associated with HSV infection as an AIDS-indicator condition.<sup>146</sup>

#### *Diagnosis*

The typical clinical appearance of HSV infections can be confirmed by isolation of virus in culture or by the demonstration by immunofluorescence of HSV 1 or 2 antigens in scrapings of skin or mucosal

lesions or by the detection of HSV DNA by PCR in the CSF of patients with suspected HSV encephalitis.

#### *Therapy*

Based on placebo-controlled studies, acyclovir is the drug of choice for treatment of infants and children. Both oral and intravenous preparations are available. Infants younger than 1 month who have HSV detected at any site should receive intravenously administered acyclovir (45–60 mg/kg per day, iv, in 3 divided doses) for 2 to 3 weeks.<sup>186</sup> Oral famcyclovir or valcyclovir may be used for treatment of adolescents (750–1500 mg/day in 3 divided doses). Patients with primary gingivostomatitis or genital HSV generally should receive oral antiviral therapy. A dose of acyclovir for uncomplicated HSV gingivostomatitis after the neonatal period has not been established; however, 80 mg/kg per day in 3 to 4 divided doses is suggested. Foscarnet (120 mg/kg per day, iv, in 2–3 divided doses until healed); cidofovir (5 mg/kg per dose, iv, once weekly for induction, then every 2 weeks for maintenance, given with probenecid); or ganciclovir (5–10 mg/kg per day, iv, once daily) may be effective in the treatment of acyclovir-resistant HSV infections.

### *Varicella-Zoster Virus (VZV)*

#### *Incidence*

In the United States, 9% of children younger than age 10 develop varicella annually.<sup>187</sup> Varicella has the potential of causing greater morbidity and mortality in immunocompromised children with HIV infection than in the general population of children.

#### *Diagnosis*

The classic clinical presentation of varicella, a generalized pruritic vesicular rash and fever, is diagnostic. If necessary, the following laboratory tests can help to confirm the diagnosis: demonstration of VZV antigens in skin lesions; isolation of virus in culture from a specimen obtained from vesicle contents (noting that VZV is difficult to grow in cell culture); a significant rise in antibody titer during convalescence; and the presence of VZV-specific IgM antibody. PCR and in situ hybridization, available in research laboratories, are extremely sensitive and specific diagnostic methods for examination of tissues suspected to be infected. Wild-type and vaccine strains of VZV can be differentiated by PCR.<sup>188</sup>

#### *Therapy*

Based on controlled trials in patients with malignancies, acyclovir administered orally (80 mg/kg per day in 4 divided doses) or intravenously (1500 mg/m<sup>2</sup> per day, iv, in 3 divided doses) should be started as soon as possible after the onset of varicella. No data applicable specifically to children with HIV infection are available. Children with low CD4+ counts at the onset of varicella infection probably are at greatest risk to develop severe infections, although many with low CD4+ counts, nonetheless, have mild infections. Given the low bioavailability of orally administered acyclovir, children with HIV infection with severe varicella (ie, those with high fever; numerous skin lesions; or deep, necrotic, or hemor-

rhagic skin lesions or visceral/systemic dissemination) should be treated intravenously.<sup>189</sup>

### Zoster

#### Incidence

Zoster occurs only in children previously infected with varicella and is unusual in children with HIV infection who sustained primary varicella infection when CD4+ levels were normal or close to normal. In children with low CD4+ counts at the time of primary varicella infection, the rate of subsequent zoster may be >50%. Retinitis is a rare complication of VZV infection in children with HIV infection; it may be confused with CMV retinitis. Progressive encephalitis attributable to VZV in the absence of a zosteriform rash may occur, but rarely.<sup>190</sup>

#### Diagnosis

The classical clinical presentation of zoster, a frequently painful vesicular eruption with a dermatomal distribution, is diagnostic. However, less typical rashes, including those that extend beyond dermatomal boundaries or that are distributed bilaterally or are generalized, also may represent zoster. If necessary, laboratory confirmation can be accomplished with virus isolation (although this is difficult to accomplish) or with detection of viral antigens in skin lesions. Zoster should be suspected in children with unilateral vesicular rashes, retinitis when CMV cannot be implicated, or progressive and otherwise unexplained encephalitis and a history of varicella.

#### Therapy

Oral acyclovir (80 mg/kg per day in 4 divided doses, maximum 4 g) may hasten healing of lesions. Given the relatively poor and unreliable bioavailability of orally administered acyclovir, zoster that fails to improve with this treatment nonetheless may respond to orally administered famciclovir (adult dose, 1500 mg/day in 3 divided doses).

Repeated courses of acyclovir therapy may be associated with emergence or acyclovir-resistant VZV. Foscarnet (120–180 mg/kg per day, iv, in 2–3 divided doses) may be useful in these circumstances. To change from acyclovir to foscarnet is a clinical decision. Although it is possible to determine the acyclovir susceptibility of VZV isolated from skin lesions, isolation of the virus is difficult and the time required to perform drug susceptibility testing limits further the clinical utility of the results.<sup>191</sup>

### Measles

#### Incidence

Measles is associated with a high morbidity and mortality in HIV-infected children.<sup>192</sup> The incidence of measles in the United States has been very low since 1992, with <1000 cases reported per year in 1993 through 1995. It is believed that indigenous transmission of measles virus was interrupted in the United States in 1993.<sup>193</sup>

#### Diagnosis

The diagnosis of measles is generally made clinically, based on the presentation with a maculopapular rash, fever, cough, coryza, conjunctivitis, and Koplik spots. Virus isolation in tissue culture is dif-

ficult and is frequently not an available diagnostic option. Fluorescent antibody testing of cells from nasopharyngeal secretions affords a sensitive means of making a diagnosis rapidly. Comparing concentrations of measles-specific antibody in acute and convalescent serum specimens or detection of measles-specific IgM antibody may help establish the diagnosis.

#### Prophylaxis

Measles-mumps-rubella (MMR) vaccine should not be administered to severely immunocompromised children with HIV infection (immune category 3). There has been one report of fatal measles vaccine-associated pneumonia in a patient with HIV infection.<sup>194</sup> Other HIV-infected and indeterminate children (immune categories 1 and 2) should receive the first dose of MMR at 12 months of age. Consideration should be given to administering the second dose of MMR vaccine as soon as 1 month (minimum of 28 days) after the first dose, rather than waiting until school entry. This will allow complete immunization at an earlier age, when the child still is capable of an adequate immune response to the vaccine.

For optimal response, administration of measles vaccine should be deferred until at least 6 months after an intramuscular dose of immunoglobulin (eg, given as postexposure prophylaxis for measles) and at least 8 months after receiving a dose of IVIG.

Administration of immune globulin (0.5 mL/kg, im) is recommended as soon as possible (within 6 days) after exposure to measles regardless of vaccination status according to many studies documenting an unpredictable response to vaccine in patients with HIV infection and reports of serious measles-associated morbidity and mortality in this population. An exception is the patient receiving IVIG at regular intervals who received a dose within 3 weeks of exposure because these preparations generally contain measles antibody at approximately the same concentration as immune globulin for intramuscular administration.<sup>192</sup>

#### Therapy

The Committee on Infectious Diseases of the AAP, WHO, and UNICEF recommend oral administration of vitamin A (100 000 IU for children 6–12 months of age, and 200 000 IU for children age 1 year and older) for treatment of measles in children with immunodeficiency including HIV infection who are not already receiving vitamin A. Several studies have documented reduced measles-associated morbidity and mortality in association with vitamin A supplementation in children in developing countries.<sup>195</sup>

Some immunosuppressed patients have been treated with ribavirin (intravenous or aerosol) on the basis of the in vitro susceptibility of measles virus to this drug, although there have been no clinical trials documenting the efficacy of this approach. Ribavirin is not approved for this indication.

### Sexually Transmitted Diseases (STD)

Most adolescents with HIV infection have been infected sexually rather than through injection or by perinatal mechanisms. Therefore, it is important to

evaluate thoroughly adolescents for other STDs.<sup>195</sup> This evaluation includes an annual anogenital examination and, for all sexually experienced females, a pelvic examination. Routine screening for STDs should include testing for syphilis, gonorrhea, chlamydia, hepatitis A and B viruses, and human papilloma virus (HPV). Cervical and anal dysplasia (and neoplasia) are significant consequences of HPV infection. Chronic and recurrent vaginal candidiasis are also complications of HIV infection in adolescent females, as is HSV infection in both males and females. Published CDC guidelines should be consulted for recommendations regarding diagnosis and treatment.<sup>196</sup>

## Management of Other Complications

### *Lymphoid Interstitial Pneumonitis (LIP)*

#### *Incidence*

LIP, also known as pulmonary lymphoid hyperplasia, is the most common cause of chronic lung disease in HIV-infected children. Before antiretroviral therapy, 25% to 40% of children with HIV infection developed LIP. The incidence of LIP appears to have decreased with increasing use of antiretroviral therapy. Nonetheless, LIP was an AIDS-indicator condition in nearly 21% of newly reported cases of pediatric AIDS in 1996.<sup>146</sup> Some children with LIP progress to chronic cystic lung disease or bronchiectasis.<sup>197,198</sup> The pathogenesis of this chronic lymphoproliferative lung disease is uncertain, although HIV and EBV both have been proposed to play an etiologic role.<sup>199</sup>

#### *Diagnosis*

LIP is characterized by the insidious onset of chronic pulmonary symptoms with mild cough and hypoxemia, often in the presence of generalized lymphadenopathy, parotid enlargement, and hepatosplenomegaly. It is most frequently seen in children older than age 1 year.<sup>200</sup> A diffuse reticulonodular pattern is seen on chest radiographs, occasionally with areas of localized consolidation. Gallium scan of the lungs may show diffuse uptake.<sup>201</sup> Definitive diagnosis can be made only with a lung biopsy demonstrating interstitial infiltration with lymphocytes and plasma cells, with or without the presence of lymphoid nodules. Other infectious and noninfectious causes of pulmonary disease should be considered part of the differential diagnosis, particularly when there is acutely worsening disease.

#### *Treatment*

LIP has long been considered to represent an indication for antiretroviral therapy, although there is no definitive evidence that antiretroviral therapy alters its course. Oxygen should be administered for hypoxemia when required. Children with an obstructive component to their lung disease may respond to bronchodilator therapy. Anecdotal reports suggest that corticosteroid therapy (eg, prednisone at 1–2 mg/kg per day for 2–4 weeks until oxygenation improves, followed by tapering to 0.5–1 mg/kg on alternate days as tolerated)<sup>200</sup> ameliorates pulmonary symptoms and oxygenation.

### *Aphthous Stomatitis*

#### *Incidence*

In a large cohort of HIV-infected adults, the prevalence of major aphthous ulcers was 3.1%. All patients had a CD4+ count <100 cells/mm<sup>3</sup>. There is no known etiology for aphthous stomatitis.<sup>202</sup>

#### *Diagnosis*

Aphthous ulcers usually present as painful shallow ulcerations on nonkeratinized oral mucosa. Other causes of ulcerations including herpes viruses, syphilis, mycobacteria, and neutropenia should be considered. Rarely, biopsy is required to distinguish aphthous ulcers from other pathologies.

#### *Treatment*

Treatment of oral ulcers varies with the cause of a given case, if such can be determined. Lacking a defined etiology, aphthous ulcers usually are treated symptomatically. Initially, such treatment may consist of topically applied dexamethasone suspension in Orabase solution.<sup>203</sup> Other therapeutic options include viscous lidocaine 2%, cimetidine, and chlorhexidine 0.12% solution. Some authorities suggest systemic prednisone therapy in patients who have recurrent major aphthous ulcers when other causes of oral lesions have been excluded.<sup>204</sup> Recently, thalidomide has been shown to be successful in the treatment of severe and refractory aphthous ulcer disease.<sup>205</sup>

### *HIV-associated Malignancies and Other Neoplasms*

#### *Incidence*

Non-Hodgkin's lymphoma is the most frequent malignancy reported to the CDC in children with HIV infection (1.5% of 6256 children reported with AIDS).<sup>206</sup> This includes Burkitt's type (0.6%), immunoblastic type (0.5%), and CNS lymphoma (0.4%). These lymphomas were reported as AIDS-indicator conditions in 1.5% of newly reported cases of pediatric AIDS in 1996.<sup>146</sup> Such malignancies frequently are associated with EBV infection, a possible causal co-factor. Kaposi's sarcoma is unusual in children with AIDS in the United States, accounting for 0% to 0.4% of pediatric AIDS-indicator conditions in recent years.<sup>145,146</sup> Other neoplasms encountered in children with HIV infection include leiomyoma and leiomyosarcoma, both of which also have been associated with EBV infection.<sup>207</sup> The Pediatric Oncology Group maintains a registry of HIV-infected children with cancer. Between 1991 and 1995, 22 children were reported, with a mean age of 8.8 years and a mean CD4+ count of 225/mm<sup>3</sup>. Physicians are encouraged to report and to refer patients to the registry by calling (312) 482-9944.

#### *Treatment*

There are no unique features regarding the management of malignancies in children with HIV infection, and principles of management are similar to those for children without HIV infection. Patients should be referred to and managed by an experienced pediatric oncologist at a tertiary care center. Clinical trial protocols for the management of lymphomas in children with HIV infection are available.

## Childhood Immunizations

HIV-infected and HIV-exposed children should be immunized according to the Immunization Schedule for HIV-Infected Children included in the 1997 *USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With Human Immunodeficiency Virus*,<sup>10</sup> and subject to routine precautions and some additional HIV-specific considerations.<sup>208</sup> Suboptimal responses to several vaccines has been demonstrated in HIV-infected children, particularly those with advanced immunosuppression.<sup>209–213</sup> However, routine serologic testing for antibody response is not recommended after any of the childhood vaccines. In regions experiencing a measles outbreak, serologic testing for measles immunity may be considered to identify susceptible children who would benefit from immune globulin prophylaxis.<sup>213–215</sup> Some pediatric HIV centers routinely assess for the presence of measles antibodies as a test of functional antibody status.

## Nutrition in HIV Infection

Worldwide, malnutrition is the most common cause of immunodeficiency and a leading contributor to childhood mortality. In children whose weight for height is normal, mortality is 0.5%, whereas in those children whose weight for height is decreased, mortality increases to >18%.<sup>216</sup> When malnutrition accompanies the immunodeficiency of HIV disease, immune function is impaired additionally. In the United States, survival in patients with HIV disease, as well as with other chronic diseases such as cystic fibrosis and cancer, is related directly to nutritional status.

In children with HIV disease, severe wasting is an AIDS-defining illness and was reported as an AIDS-indicator condition in 17% of children with AIDS in 1996.<sup>146</sup> In a multicenter trial evaluating the effects of ZDV on childhood HIV, 80% of the children with HIV infection had weight-for-age less than the 25th percentile.<sup>62</sup> Other studies have demonstrated that decreases in weight and height percentiles begin within the first 6 months of life.<sup>217</sup> Therefore, impaired nutritional status may reflect viral activity early in life, before more obvious sequelae of HIV disease develop. Recognition by health care providers of the importance of nurturing and nutrition should increase awareness and anticipation of clinical situations that may potentially impair availability, absorption, or utilization of sufficient nutrients.

Appropriate nutrition is a fundamental and necessary part of a child's medical therapy. Nutrition impacts on the management of children with HIV infection by affecting gastrointestinal tract function, CNS development, immune function, recovery from infection, bioavailability of therapeutic agents, growth, and quality of life. Because of these multiple effects, nutritional support should be an integral part of any therapeutic intervention for mothers and children with HIV disease. A team of providers with multidisciplinary skills is required for optimal management. For HIV-infected children whose parents

(virtually all living biological mothers) may have chronic disease, the nutritional status of the nurturing parent impacts on family health and cannot be ignored when developing a care plan for a child. Families affected by HIV may experience chronic and recurrent stress related to deaths of family members, poverty, social isolation, substance abuse, and discrimination. Instead of being the recipient of support and nurturing, children with HIV-infected parents may find that they are these parents' prime source of support.<sup>218</sup>

## Diagnosis of Altered Nutritional Status, Malnutrition, and Wasting Syndrome

Growth delay affecting both height and weight is one of the earliest effects of HIV disease in infants and children. Serial measurements of height, weight, and head circumference are an essential component of diagnosis. Nutrition intervention should begin before a child is malnourished. Preventive measures should be taken at the onset of alterations in nutritional status. Altered nutritional status for children with HIV infection is defined by 1) weight growth velocity that is <5% for >2 months; 2) a decrease in one major growth percentile channel for weight; 3) weight percent standard or weight-for-height percent standard that is <90%; 4) weight for height that is <5%; 5) a loss of >5% of lean body mass; or 6) serum albumin that is <3 g/dL.<sup>219</sup>

The diagnosis of malnutrition can be made simply by determining accurately weight and height and weight-for-height percentile. Malnutrition is classified as mild, moderate, or severe based on height and weight parameters for age as described by Waterlow.<sup>220</sup> Children who are 90% to 100% of standard (50th percentile) weight-for-height are normal; children who are 80% to 90% of standard weight-for-height are mildly malnourished; children who are 70% to 80% of standard weight-for-height are moderately malnourished; and children <70% of standard weight-for-height are severely malnourished.

Wasting syndrome is defined by the CDC as 1) persistent weight loss >10% of baseline; 2) downward crossing of at least two of the following percentile lines on the weight-for-age chart (eg, 95th, 75th, 50th, 25th, 5th) in a child 1 year of age or older; or 3) <5th percentile on weight-for-height chart on two consecutive measurements  $\geq 30$  days apart, in addition to chronic diarrhea (ie, at least two stools per day for  $\geq 30$  days) and documented intermittent or consistent fever for  $\geq 30$  days. These signs and symptoms should not be attributable to any concurrent illness.<sup>221</sup>

## Guidelines for Evaluation of Nutritional Status

### *Longitudinal Assessment of Growth*

The most readily available parameters to assess a child's nutritional status are accrual of weight, height, and head circumference. Parental stature and intrauterine growth, reflected by birth weight and length, also are relevant considerations.

### Estimating Energy Requirements

Asymptomatic adults with HIV infection have increased resting energy expenditure and total energy expenditure,<sup>222</sup> but preliminary data in children with HIV infection suggest that resting energy expenditure is not increased in those children with failure to thrive.<sup>223</sup> Clinical experience suggests that energy requirements are normal during times of well-being, but that the child with HIV infection may not compensate for periods of stress (eg, infection) when energy requirements are increased.

The Recommended Daily Allowance (RDA) is the most convenient standard for determining caloric needs. Alternatively, resting energy expenditure plus activity or stress factors (eg, febrile illness) could be used to estimate energy requirements, although the specific energy requirements, engendered by HIV infection itself, are not yet known. During times of stress, caloric requirements may increase to 150% of the RDA.

RECOMMENDED DAILY ENERGY AND PROTEIN INTAKE BY AGE<sup>224</sup>

Age (years)	Kcal/kg	Protein/kg (grams)
0-0.5	108	2.2
0.5-1.0	98	1.6
1-3	102	1.2
4-6	90	1.1
7-10	70	1.1
11-14 (males)	55	1.0
11-14 (females)	47	1.0
15-18 (males)	45	0.9
15-18 (females)	40	0.8

### Evaluating Body Composition

In HIV-infected children, lean body mass appears to be lost in favor of fat mass. The reasons for this alteration in body composition are not clear. Some laboratory studies may be helpful in evaluating nutritional status. Nutritional protein status can be determined most reliably by measuring proteins with relatively short half-lives such as prealbumin or retinyl-binding protein. Measures of hematocrit, T-cell immune status, and specific minerals or vitamins may be of benefit in specific situations. Bioelectrical impedance is another simple method to determine body composition. Although there is limited information regarding reliability in children, equations have been developed for children with HIV infection.<sup>225</sup> Body composition, such as total body bone mineral content, body fat content, and fat-free mass, can be measured using dual x-ray absorptiometry (DEXA), the standard by which other body composition methods are evaluated.<sup>226</sup>

### Dietary Assessment

Health care providers often encounter difficulties when they attempt to measure caloric intake. Both the 72-hour diet diary and the 24-hour diet recall are inadequate. Nevertheless, estimation of caloric intake and assessment of available food resources should be part of a complete evaluation. A comprehensive diet history should include an evaluation of several factors including: 1) caloric intake; 2) symptoms of gastrointestinal disturbances (eg, anorexia,

nausea, vomiting, diarrhea, early satiety, heartburn, fever); 3) access to food (including the availability of electricity, refrigeration, cooking utensils, resources for food transportation); 4) typical diet including type of formula, other liquids/foods provided, meals eaten in/out of home, beverages consumed at meals and as snacks; 5) food safety (ie, facilities for cleaning bottles, nipples, and utensils; education about discarding formula that has been at room temperature for >8 hours; mixing formula for 1 day only; washing hands before food preparation; cooking meat well; and avoiding uncooked eggs and other raw foods). The food sufficiency questionnaire will assist in identifying children receiving insufficient and/or inappropriate diets.<sup>227</sup> This type of instrument can be used by home-visit nursing service.

### Evaluation of Micronutrients and Vitamins

Children with delayed growth or malnutrition should be observed for clinical signs and symptoms of vitamin and/or micronutrient deficiencies. Iron, carnitine, and vitamin A deficiencies also impact on immune function and measures should be evaluated in the HIV-infected child who is not achieving expected growth milestones or has other signs or symptoms of possible deficiency. Deficiencies of other micronutrients and vitamins such as zinc, selenium, and vitamin D are less common in US children with HIV infection.

### Role of Parental Health

The health and nutritional status of the nurturing parent is linked directly to that of the child. If the parent is HIV-infected, anticipation of her/his health care needs, including nutritional support, should be an ongoing consideration in the child's management. Developmental delays and absence of a primary caretaker have been reported with greater frequency in children with perinatal HIV and failure to thrive.<sup>228</sup> Hence, efforts to support parent-child relationships and screening for developmental delays are essential components of prevention.

### Role of Chronic/Recurrent Infection

Recurrent or chronic infection increases metabolic needs. If the child is febrile, caloric demands are significantly higher. Intestinal infections not only increase nutrient requirements, but may decrease intake and impair absorption. *Candida* esophagitis may cause pain with swallowing, resulting in decreased oral intake primarily for solids, but also for liquids. Cryptosporidiosis or other enteric pathogens cause diarrhea by injuring the intestinal brush border and impairing absorption of carbohydrates, proteins, fats, and other essential nutrients. Enteric infection can be prevented by avoiding ingesting contaminated water or ice, swimming in contaminated lakes or beach water, and eating undercooked meat.

### Treatment of Nutritional Deficiency

The approach to maximizing nutritional support and avoiding malnutrition in children with HIV infection is accomplished by attention to the following goals of nutritional management: 1) treat underlying

gastrointestinal or infectious diseases that interfere with nutrient intake, absorption, or increase nutrient loss; and 2) provide sufficient nutrition for catch-up growth.

#### *Oral Supplementation and Dietary Management*

The goals outlined above can best be realized when nutritional services are provided in a proactive manner including the use of enteral supplements. These supplements should be initiated early to prevent sequelae of malnutrition while increasing overall intake through more frequent feedings, use of concentrated formulas and calorically dense foods, and providing specific nutrients (vitamins and minerals). Specific examples of oral enteral supplements for children age 1 to 20 years include Pediasure, Kindercal, Nutren Jr (isotonic, intact supplements), and Peptamin Jr (a semielemental product for children with malabsorption). Children with HIV infection may develop lactose intolerance earlier than predicted by genetic predisposition. Lactose-free diets are preferred for these children. For children with significant chronic diarrhea without an identifiable cause, lactose-free diets, lactase supplements, soluble fiber, medium chain triglycerides or protein hydrolysate formulas may be better absorbed. Oral and esophageal lesions can result in decreased caloric intake and can be managed by eating soft, warm, or cool foods; avoiding salty, acidic, or spicy foods; and/or using topical anesthetic agents such as benadryl or lidocaine swishes before meals.

#### *Tube Feeding*

Nasogastric or gastrostomy feedings are indicated if oral dietary management fails to promote weight gain. Although there are no specific standards, most nutritionists would initiate tube feedings when the weight or weight-for-height percentile standard is <80%. Although children with higher CD4+ counts have a better response to caloric supplementation, there are no data showing that intensive enteral nutrition support alone results in significant long-term nutritional improvement and growth.<sup>229</sup> Tube feedings increase fat mass but may not significantly increase lean body mass.<sup>230</sup> Nasogastric tube feedings are painful, increase the possibility of sinusitis, and limit oral intake. Nevertheless, they can serve as an initial means to evaluate the potential efficacy of long-term gastrostomy tube feedings. Gastrostomy tube buttons can be placed safely endoscopically, provide access for enteral support, and do not restrict normal activities. Although problematic, tube feedings via gastrostomy tube buttons can result in improved quality of life in children with nutritional disturbances.

#### *Parenteral Feeding*

Total parenteral nutrition (TPN) should be restricted to those children who are unable to tolerate sufficient enteral nutrition to maintain appropriate growth parameters. Because of its expense and the risks of in-dwelling catheters, TPN should be reserved for children with severe nutritional disturbances. Children with HIV infection, despite immu-

nocompromise, may benefit from total parenteral nutrition and not experience an increase in catheter-associated infection.<sup>231,232</sup> Even after TPN has been initiated, efforts should be made to continue enteral nutrition in some capacity to maximize the functional integrity of the gastrointestinal tract, provide oral gratification, and gain the psychosocial benefits of a defined meal.

#### *Appetite Stimulants and Growth Hormone*

There have been few pediatric studies of the use of appetite stimulants. Some specialists in the care of HIV-infected children have noted that there is a return in appetite and weight gain in some children treated with nonspecific (eg, corticosteroids, cyproheptadine) or specific appetite stimulants (eg, megestrol acetate [Megace], dronabinol). Megace provides weight gain primarily by increasing fat mass. Lean body mass may be increased less significantly.<sup>233</sup> There are almost no data on the use of this progestational hormone in children; however, one recent study demonstrated significant weight gain at a dose of ~8 mg/kg per day. Body composition was not assessed, and linear growth was not observed. Weight gain was not sustained or weight loss recurred when the medication was no longer administered.<sup>234</sup> Dronabinol has psychological side effects that may limit its use in children.

In HIV-infected adults, recombinant human growth hormone therapy results in increased body weight and lean body mass. Growth hormone therapy is a potentially beneficial therapeutic intervention in HIV-infected children or adolescents who have decreased linear growth or diminished lean body mass. Increases in lean body mass observed in adults should be expected to occur in the pediatric population. Growth hormone accelerates bone age commensurate with height; whereas, other anabolic agents accelerate bone age out of proportion to linear growth. This characteristic makes growth hormone particularly well suited for use in children. Because of the expense of this therapeutic intervention, it should be evaluated initially in a controlled clinical trial.<sup>235,236</sup>

#### **Summary**

Nutritional intervention should be integrated into the care plan for all HIV-exposed and -infected children. Because nutritional issues affect the entire family, to have an impact, therapy must be directed at the family unit. Efficacy of medical treatment and quality of life are improved by developing a nutritional strategy that maintains appropriate growth and physical activity. These guidelines are intended to provide a basis for intervention; however, for implementation, they require the participation of a multidisciplinary team including nurses, nutritionists, pharmacists, physicians, and social workers.

#### **Neuropsychological Complications of HIV Infection**

##### *Neurologic Complications*

HIV-associated neurologic disease in children, known as HIV-associated progressive encephalopa-

thy (PE), is the clinical corollary of the direct and indirect effects of CNS and/or systemic HIV infection and is analogous to the process seen in adults called AIDS dementia complex (ADC).<sup>237-239</sup> PE has an estimated prevalence of 13% to 23% in pediatric patients.<sup>239,240</sup> There is often a more rapid clinical presentation of PE in infants and young children compared with the long latency typically seen before the onset of neurologic disease in adults, at least in part because of the increased susceptibility of the CNS to infection at early stages of fetal brain development.<sup>241</sup> Timing of infection (fetal versus intrapartum), virulence of the acquired viral strain, and other poorly understood immune factors may account for variations in the clinical rapidity and bimodal expression of clinical symptomatology often observed in infants.<sup>242</sup> In areas of the world where horizontal infection of children predominates and in studies of neonates and hemophiliacs infected via blood transfusions or contaminated factor VIII, the incidence of HIV-associated neurologic disease is much lower, or disease more latent, adding additional credence to the hypothesis that the CNS is more susceptible to virulent infection during fetal development.<sup>243,244</sup> However, there exist subpopulations of children with perinatally acquired HIV infection who also have a prolonged asymptomatic phase before the onset of encephalopathy. Also, as with ADC, PE often is associated with immune deficiency, but is not directly correlated to CD4+ lymphocyte counts, although there is a suggestion that there may be a relationship to CSF viral burden.<sup>245</sup>

Static encephalopathy (SE) can also occur in children with HIV infection and represents fixed, nonprogressive neurologic or neurodevelopmental deficits, often related etiologically to identifiable historical insults, such as prematurity, intrauterine exposure to toxins or infectious agents, genetic factors, or head trauma. It is unclear whether HIV infection of the CNS is the primary causative or a contributing factor to SE or whether SE results solely from non-HIV-related neurologic insults. Children with HIV infection and SE may improve spontaneously with time, may follow a static course, or may experience neurologic decline/PE.<sup>237-239</sup> An infant of an HIV-infected mother who presents with significant neurodevelopmental delay should suggest that this abnormality may represent the beginning of HIV-related neurologic disease such as PE. Clinical neurologic correlation and laboratory investigation to assess for systemic and CNS HIV infection should be pursued.

Thus neurologic disease in infants, children, and adolescents with HIV infection has a major impact on their quality of life and management decisions. The assessment of neurologic function also has evolved as an important surrogate marker of antiretroviral drug efficacy (Table 12).

#### *Clinical Features of HIV-associated PE*

The predominant clinical neurologic findings of PE seen in the pediatric population with HIV infection consist of a well defined triad: 1) impaired brain growth, determined by serial head circumference

measurements (in children younger than age 3) or by progressive brain parenchymal volume loss on serial neuroimaging studies (atrophy); 2) progressive motor dysfunction; and 3) loss or plateauing of, or inadequate rate of achieving, neurodevelopmental milestones.<sup>246</sup> In the child who is neurologically normal at baseline, progression in one of the three conditions; or in the child who is neurologically abnormal at baseline, progression in two of the three conditions, constitutes the bases for a clinical diagnosis of PE or disease progression.

#### *Impaired Brain Growth*

Children with PE often experience an impairment of brain growth, which is observed clinically and has been confirmed in various neuropathologic studies.<sup>237-239</sup> Because the rapid head growth velocity seen in infancy results from expansion of brain volume, a plateauing of or decrease in serial measurements of head circumference velocity for children younger than age 3 is a reflection of impaired brain growth. In the older child with closed skull sutures, head circumference velocity has slowed; thus, an inordinately prolonged interval must pass before any change in or plateauing of velocity can be detected. Consequently, in this older age group (or to confirm a suspicion of impaired brain growth in an infant), serial computed tomography (CT) or magnetic resonance imaging (MRI) can be used to detect progressive loss of brain parenchymal volume.

#### *Progressive Motor Dysfunction*

Progressive motor dysfunction should be carefully distinguished from the nonprogressive motor deficits seen in SE. Motor deficits usually result in impairment of fine motor function and eventually gross motor skills, and often observed gait disturbances result primarily from pyramidal or extrapyramidal dysfunction rather than from cerebellar involvement.<sup>237,247</sup> Hyper- or hypotonia is apparent, and spasticity is common. Motor deficits are usually symmetric; the onset of focality, even if superimposed on a background of spasticity, should suggest a structural cerebral lesion, such as a mass lesion or infarct. Significant motor milestones are not achieved or, if attained previously, are lost. In severe cases, previously ambulatory and functional children become spastic and nonambulatory and require assistance in activities of daily living. Some children with PE can display elements of an extrapyramidal syndrome (EPS) manifesting as rigidity, dysarthria with drooling, hypomimetic facies, and gait disturbances that may be ameliorated by levodopa therapy.<sup>247</sup>

#### *Neurodevelopmental Decline*

Loss or plateauing of neurodevelopmental milestones or a significant deterioration on psychometric measures is a frequent concomitant to clinical neurologic decline associated with systemic HIV disease progression.<sup>248</sup> Developmental, cognitive, and behavioral functioning can be influenced by many confounding factors including environmental, psychosocial, and nutritional factors, although their contributions to the level of functioning in children with severe encephalopathy are limited.<sup>248</sup> Psychometric testing has proven very useful in quantifying

both initial levels of functioning in infants and children with HIV disease as well as in documenting interval change. It would be useful to have neuropsychometric markers presaging the onset of clinical neurologic disease in otherwise asymptomatic children with HIV infection; however, as yet no specific set of tests or measures has been predictive of PE in otherwise asymptomatic children.

### Neurologic/Psychometric Testing

Psychometric/neurodevelopmental/neurobehavioral testing of infants and children should be correlated with clinical neurologic, neuroimaging, and laboratory assessments. Periodic evaluations are integral to the care of pediatric patients with HIV infection, especially those with neurologic abnormalities or developmental delays, or those receiving antiretroviral therapy. Psychometric evaluations should be performed or supervised by a licensed psychologist, preferably one with experience in the social and medical confounders often present in this population, using standardized tests of global mental abilities with reliable age norms. Scheduling follow-up testing will require adaptation to the particular circumstances of the patient and resources available in a particular geographic region. However, because neurologic surrogate markers are important for treatment decisions, ideally the schedule outlined in Table 17 should be considered. To reduce the burden of testing, there can be some consideration for using more abbreviated testing tools, such as screening devices, and more extensive assessments if a problem is identified. If PE is suspected, confirmatory adjunctive testing should be considered (Tables 12, 17).

### Other Neurologic Disorders

There are other noteworthy neurologic disorders that occur in association with HIV infection. It is imperative to differentiate those resulting from HIV infection or associated immune deficiency from secondary opportunistic infection (OI), other organ sys-

tem dysfunction, or etiologies unrelated to HIV infection.

### Seizures

Seizures, particularly of partial/focal onset, raise particular concerns for underlying focal cerebral pathology, such as mass lesion, infarction/stroke, or infectious process.<sup>237</sup> If a seizure is manifest, a neuroimaging study is indicated to identify any focal neurologic pathology or concomitant evidence of PE. If a CNS inflammatory or infectious process is suspected and there are no contraindications to performing a lumbar puncture, examination of the CSF may be useful.

### Cerebrovascular Disease/Stroke

Strokes have been reported surprisingly less often than might be expected, considering the extensive HIV-related cerebrovascular pathology uncovered at autopsy.<sup>249</sup> Extensive investigation of stroke events is necessary to differentiate processes not resulting directly from HIV infection, especially concomitant cardiogenic or CNS infectious, inflammatory, vasculitic, oncologic, hematologic, or metabolic mechanisms.

### Myelopathies

Vacuolar myelopathies and other spinal cord pathologies are found in up to 30% of HIV-infected adult postmortem specimens, but they are rarely expressed clinically in children. Often they result from a reactivated infection such as measles or CMV.<sup>249</sup> Spinal cord syndromes can be clinically evident but, on occasion, spinal cord pathology is discovered only at postmortem examination.

### Neuromuscular Disorders

HIV-associated painful neuropathies and myopathic syndromes are prevalent in adults in whom they are a source of major morbidity; they are rarely observed in the pediatric population. When presented with a neuropathy or myopathy, it can be

**TABLE 17.** Recommended Schedule of Neurologic/Psychometric Testing for Children With HIV Infection

Test	Baseline	<1 Y	1–3 Y	3–10 Y	>10 Y
Psychometric <sup>a</sup>	x	q3–4 mo	q6mo <sup>c</sup> q3–4mo <sup>d</sup>	yearly <sup>c</sup> q4–6mo <sup>d</sup>	q2years <sup>c</sup> q4–6mo <sup>d</sup>
Neurologic <sup>b</sup>	x	q3–4 mo	q6mo <sup>c</sup> q3–4mo <sup>d</sup>	yearly <sup>c</sup> q4–6mo <sup>d</sup>	yearly <sup>c</sup> q4–6mo <sup>d</sup>
MRI/CT CSF	Consider <sup>e</sup> <sub>f</sub>	Consider <sup>e</sup> <sub>f</sub>	Consider <sup>e</sup> <sub>f</sub>	Consider <sup>e</sup> <sub>f</sub>	Consider <sup>e</sup> <sub>f</sub>

<sup>a</sup> Use standardized and quantified psychometric tests of global mental ability with reliable age norms; testing should be administered by a licensed psychologist. Declines of  $\geq 2$  SD units (<3 years old) or  $\geq 1$  SD unit (>3 years old) should be confirmed with repeat testing in 1 month.

<sup>b</sup> Clinical neurologic examinations should focus on measures of head circumference (<3 years) and motor function. Significant decreases in head circumference velocity or loss of parenchymal volume on serial neuroimaging should be confirmed with repeat measures/studies in 2 months; clinical motor dysfunction should be confirmed in 1 month.

<sup>c</sup> Neurologically/neurodevelopmentally normal or static/nonprogressive deficits.

<sup>d</sup> Neurologically/neurodevelopmentally abnormal with progressive deficits.

<sup>e</sup> Particularly useful if there is a decrease in head circumference velocity or if there are significant motor abnormalities or focality on clinical neurologic examination. The interval of repeat neuroimaging studies will depend on the individual clinical situation, but can be helpful in making treatment decisions.

<sup>f</sup> No specific recommendations can be offered at this time, but there is growing evidence that HIV PCR of the CSF may be a useful adjunctive surrogate marker of neurologic drug efficacy and/or neurologic disease progression/improvement.

difficult to differentiate the potential etiologies including HIV and secondary infectious/parainfectious or metabolic processes. In addition, antiretroviral drug toxicity is implicated increasingly as a primary etiologic mechanism (Table 8).

ZDV-associated myopathy has been reported in children.<sup>250</sup> This entity has been shown to result from mitochondrial dysfunction/pathology, and laboratory evidence suggests that carnitine supplementation can ameliorate in vitro findings, but clinical trials are presently ongoing.<sup>251</sup>

Painful HIV-associated neuropathies have not been well defined in children. However, neuropathies can be a complication of nucleoside analogue therapy (particularly associated with ddI, ddC, or d4T) or of an OI such as CMV. Relief usually occurs with cessation or dose reduction of the drug. However, pain may continue for weeks after discontinuing the offending nucleoside analogue because of the coasting phenomenon.

#### CSF

The CSF profile is rather nonspecific, even in consideration of florid PE. There may be mild elevations in cells or protein, but also the CSF may be normal. However, there is recent evidence that HIV-1 RNA levels in CSF may be useful as an adjunct to establishing the diagnosis of PE and in making treatment decisions.<sup>245</sup> In consideration of acute or chronic CNS or meningeal infection/inflammation, appropriate changes in the CSF formula are usually observed. However, in cases associated with severe immune compromise, an appropriate inflammatory response may not be mounted.

#### Psychiatric and Behavioral Manifestations

There is increasing evidence of significant neurobehavioral aberrations in HIV-infected children.<sup>248</sup> As in adults, overt symptoms are likely attributable to organic pathology of the CNS, particularly if associated with clinically diagnosed PE or a concomitant CNS OI. However, a significant portion of overt psychiatric symptoms in children likely results from reaction to chronic illness, environmental and social issues, familial or genetic predisposition, SE, or drug toxicities. Frank psychosis or primary depression is rarely reported in children but may be underrecognized. Autistic symptomatology in children with PE also has been described. Emotional and behavioral manifestations of HIV in preschool and school children are predominantly disorders of attention, particularly attention deficit/hyperactivity disorder (ADHD), but also may include depression, anxiety, adjustment disorders, and learning disabilities.<sup>248</sup> Coping with their own chronic illness, and often that of other family members as well, adds emotional and behavioral stress to the lives of children with HIV infection.

#### Acute Psychosis and Mental Status Changes

Although rare, acute psychosis can often complicate the end-stages of disease in children with HIV infection. Psychotic behaviors (confusion, agitation, delirium, mania, and catatonia) can result from nu-

tritional deficiencies, intercurrent infections (such as CMV encephalitis), PE, or the toxic effects of various drug treatments. Any acute change in behavior or mental status, particularly if accompanied by lethargy, headache, or seizures, may be attributable to metabolic derangements, toxic substances, nutritional deficiencies, increased intracranial pressure from mass lesions or other causes, or infectious complications/OI involving the CNS.

#### Depression

In children and adolescents with HIV infection, depression can develop in response to the condition of chronic illness and, frequently, to associated family dysfunction or illness. CNS HIV infection also may contribute to an organic depression. Apathy, social withdrawal, and anorexia are some of the manifestations of depression in chronic illness; however, at times it may be difficult to distinguish these symptoms from those attributable to the organic effects of HIV or OI. Depression can lead to significant noncompliance with medications and other medically required regimens. In assessing a child with a marked depressive affect, unless a psychosocial precipitant or CNS organic etiology can be identified, there should be a careful assessment of nutritional needs and consideration of metabolic or endocrine disturbances, particularly thyroid dysfunction, as alternative explanations.

#### Disorders of Attention

Children with HIV infection manifest a high incidence of traits compatible with a diagnosis of ADHD.<sup>248</sup> In otherwise neurologically asymptomatic children, a causal relationship between HIV and attentional deficits or hyperactivity is not established clearly. Other identifiable risk factors in the prenatal/perinatal/family/environmental histories, or external factors, such as lead poisoning, may be more contributory than HIV. However, ADHD may result from structural changes within the white matter, as are seen with PE.<sup>248,249</sup>

#### Learning Disorders/Educational Issues

There are numerous reasons and contributors to academic difficulties commonly seen in children with HIV infection. Often they include genetic, familial, and environmental issues not directly related to HIV, as well as school absenteeism. However, HIV-associated CNS disease is highly associated with cognitive deficits, which frequently lead to subsequent learning difficulties.

#### Treatment of Neuropsychological Complications of HIV Infections

As it has become clear that a significant number of children with HIV/AIDS develop clinical neurologic and behavioral difficulties, it has become necessary to develop treatment regimens that are effective and safe in the CNS/peripheral nervous system, as well as are effective prophylactic regimens. Antiretroviral drugs are also essential in reversing the ravages of PE, but other adjunctive nonpharmacologic and nu-

tritional therapies are important in improving the quality of life of these children.

### Treatment of CNS/PNS Complications

#### *Antiretroviral Drugs*

Early studies of monotherapy found that in PE, intermittent oral or continuously infused ZDV caused dramatic cognitive/psychometric, clinical, radiologic, and virologic improvements over the first 6 months of therapy.<sup>62,252</sup> However, the effect was not sustained in all children, and after initial improvement, a significant number of children with PE were observed to deteriorate on long-term therapy, probably because of the development of resistance.<sup>253</sup> Nevertheless, there are encouraging data that suggest that various combinations of nucleoside analogues, particularly ZDV/ddI and ZDV/3TC, are efficacious in reversing HIV-associated neurologic complications. The efficacy of PI or NNRTI agents in ameliorating CNS disease has not yet been established, although data from clinical trials will be forthcoming.

The guidelines concerning the use of antiretroviral agents in pediatric patients with PE conform to the general management guidelines. However, given the proven efficacy of ZDV in PE, if the patient is drug-naïve to ZDV, a combination antiretroviral regimen that includes ZDV should be chosen. In a child already receiving ZDV who develops neurologic deterioration, the general guidelines for changing therapy should be followed. Additional research should help determine the most neuroprotective regimen in patients without PE.

#### *Rehabilitation*

Many children with PE require extensive physical and occupational therapy. Patients presenting with EPS may benefit from levodopa therapy, with improvements in ambulation, activity levels, facial expression, and swallowing, and reduced rigidity and drooling.<sup>247</sup> In cases of severe spasticity with tendon contractures not amenable to physical therapy or splinting alone, pharmacologic antispastic agents (such as benzodiazepines or baclofen) can be useful and, on occasion, botulinum toxin, ethanol nerve blocks, and surgical tendon lengthenings may also be beneficial. All infants and children with HIV infection who also have fine and gross motor impairments can benefit from physical and occupational therapy. Speech pathologists can also assist patients with feeding difficulties, dysarthria, or language deficits.<sup>239</sup>

#### *Nutritional/Metabolic Therapies*

Optimizing of nutritional status is important for maximizing neurologic functioning (see "Nutrition in HIV Infection.") Deficiencies of certain nutrients can have devastating effects on the CNS, such as the development of Wernicke's encephalopathy in patients with thiamine deficiency.<sup>239</sup>

#### *Immunomodulatory Therapy*

There has been a growing interest in alternative and adjunctive therapies that can boost and reconsti-

tute a compromised immune system, enhance intrinsic immune defenses directed against HIV, or modulate secondary cytotoxic pathways unregulated and stimulated by HIV.<sup>239</sup> Results from some early trials in adults using the cytokine modulator pentoxifylline have been disappointing, although therapies that may be neuroprotective, such as *N*-methyl-D-aspartate (NMDA) antagonists, have shown early promise. In PE, there is anecdotal evidence of steroid efficacy, although controlled studies are lacking. However, side effects may limit their use.<sup>254</sup> Other potential adjunctive therapies for PE have not been studied specifically in the pediatric population.

### Treatment of Psychiatric and Neurobehavioral Complications

The treatment of psychiatric and neurobehavioral problems represents a difficult but essential task. In addition to improving a child or adolescent's overall quality of life, when effective, such treatments afford additional benefits including those that accrue to improved compliance with treatment regimens and better adherence to reducing high-risk transmission behaviors.

#### *Psychotherapy*

Short-term psychotherapy is indicated in assisting children and adolescents deal with psychologic traumas such as family death or sexual abuse; long-term psychotherapy may be necessary to better enable children to confront the issues of chronic illness and social stigma associated with HIV infection. Both individual and family therapy may be required. For nonverbal children, or for those with significant neurologic impairment, behavioral modification therapies may be more useful. Psychotherapy is a necessary component of treatment of depression and psychosis.

### Psychoactive Medications

#### *Antidepressants*

Although psychotherapy is often the standard of therapy for children with depression, on occasion children may benefit from antidepressants if there is no medical contraindication to their use. Tricyclic antidepressants can have synergist effects with opioids in the management of severe pain in children. Attention must be paid to potential interactions between psychotropic and PI agents.

#### *Neuroleptics*

Low-dose neuroleptics may be helpful in PE, as they are in some children who are developmentally disabled or brain-injured with mental retardation, or those who display autistic traits, aggressive, or self-injurious behaviors.<sup>239</sup> However, intensive behavioral modification programs may offer an important additional or alternative therapeutic modality. Acute psychosis may respond to neuroleptic treatment. However, of note, the patient with PE or ADC may be somewhat more susceptible to neuroleptic side effects than the usual recipient.<sup>239</sup>

Psychostimulants such as methylphenidate (Ritalin) are very useful in managing attentional deficits with or without hyperactivity and often are efficacious in low doses. A treatment course can be useful in enhancing and maximizing the child's academic and behavioral potential. However, as in all children with ADHD, underlying precipitants should be eliminated and behavioral modification techniques should be considered before medication and always implemented in addition to a pharmacologic regimen. Appetite suppression with stimulants can be an undesirable side effect, particularly in patients with poor weight gain. Adolescents with clinical depression and a lack of energy or psychomotor slowing may respond to methylphenidate.<sup>239</sup>

### Summary

In addition to severe immune deficiency and multorgan dysfunction, CNS impairment is a major consequence of HIV infection; infants and children are uniquely at risk for the encephalopathic effects of HIV, particularly if infection occurs during early stages of fetal or neonatal brain development. There is a wide spectrum of neurologic and behavioral manifestations of PE, but alternative underlying non-HIV conditions must be considered in the differential diagnosis. Although rare in infants and young children, CNS OI also can precipitate neurologic or psychiatric dysfunction or may mimic or confuse the diagnosis of PE. PE is a clinical diagnosis established by serial psychometric testing and clinical neurologic examinations and may be supported by neuroimaging, immunologic, and virologic studies; such tests and evaluations also are important surrogate markers for antiretroviral drug efficacy. Table 17 summarizes the recommended schedule for psychometric and neurologic studies.

Antiretroviral therapies available currently have proven efficacy in improving neurologic manifestations of HIV. However, some debilitating neuromuscular toxicities have been reported. As antiretroviral therapies improve, the CNS may become an important harbor for HIV viral particles that elude elimination or suppression. Such scenarios will only add to the growing need for developing innovative adjunctive therapies directed at specific neuropathogenic pathways. There has been a gratifying overlap in preventing certain CNS OI with systemic OI prophylaxis; however, individual cases may need specific CNS OI prophylaxis/treatment.

In addition to implementing antiretroviral therapy and OI prophylaxis/treatment, attention should be given to maximizing motor and language function, alleviating pain, integrating in the educational setting when possible, and instituting psychotherapy and/or psychoactive medications when needed. Adverse behavioral patterns may respond to combinations of behavioral modification regimens and drug therapies; underlying treatable causes should be explored. Correction of nutritional deficiencies and, in certain cases, supplementation, is essential. As the pendulum of the epidemic has swung from dying with AIDS to living with HIV infection, diagnostic

studies and therapeutic interventions must be tempered carefully with maximizing quality of life.

### Palliative Care and Pain Management in HIV Infection

Children who have HIV infection, regardless of the stage of illness, complications, or goals of care, often are highly symptomatic. An evolving discipline, pediatric palliative medicine is focused on the management of the physical, psychological, and spiritual problems inherent in life-threatening illnesses regardless of these variables. Pain management for children with HIV infection is one component of a comprehensive program providing palliative care for these children.

#### *Pain Syndromes in HIV Infection*

The prevalence of pain in an inpatient population of children with HIV infection has been reported to be 88%,<sup>255</sup> and 59% of outpatients reported pain as having a negative impact on their lives.<sup>256</sup> Children with HIV infection may experience pain from medical procedures or pain syndromes related to somatic pain (eg, arthritis/arthralgia, myositis/myalgia); visceral pain (eg, pharyngitis, esophagitis, enteritis, diseases of the biliary tract, liver, and pancreas); neuropathic pain (eg, neuropathy related to HIV or other infections, antiretroviral or other antimicrobial therapy); or other HIV-associated pain (eg, headache).

#### *Pain Management Strategies in HIV Infection*

An aggressive approach to pain management in children with HIV infection is recommended, using a combination of pharmacologic and nonpharmacologic therapies. The reader is referred to other sources of information regarding the latter.<sup>257</sup>

##### *When to Initiate Analgesic Therapy*

Analgesic therapy is initiated after a clinical assessment, including an assessment of pain severity, has been made and treatment of the underlying cause of pain implemented. Chronic pain in children may manifest as depressed affect, inactivity, anorexia, and so forth, rather than by behaviors that are more obviously indicative of pain. The World Health Organization analgesic ladder recommends analgesic prescription according to pain severity, ranging from nonopioid analgesic drugs for mild pain to opioids for severe pain, and the use of adjuvant analgesic agents, when appropriate, irrespective of pain severity.

##### *What Drugs/Doses/Schedules to Use When Therapy Is Initiated*

Standard dosing schedules of analgesics should be used (Table 18).<sup>258</sup> Unless a child's episodes of pain are incidental or unpredictable, or there is some other contraindication, analgesics should be administered at regular times, by the clock, to prevent breakthrough pain. If pain is a cause of sleep disturbance, a prescription of a larger dose of opioid at bedtime or the use of sustained release preparations (eg, MS-Contin) will reduce the chance of awakening from pain at night. The chronic use of meperidine (Demerol) should be avoided because of the potential neurotoxic side effects of this agent.

**TABLE 18.** Suggested Protocol for Pharmacologic Management of Pain in HIV-infected Infants and Children

Pain	Medication	Starting Dose, Route, and Frequency
Mild pain <sup>a</sup>	Acetaminophen	10–15 mg/kg po q4h 15–20 mg/kg rectally q4h
	Choline–magnesium trisalicylate	10–15 mg/kg po q6–8h
	Aspirin	10–15 mg/kg po q4h
	Ibuprofen	10 mg/kg po q6–8h
	Naproxen	5 mg/kg po q8–12h
Moderate pain <sup>b</sup>	Continue above and ADD weak opioid Codeine	1 mg/kg po q3–4h
Severe pain	Continue nonopioid medication if tolerated and ADD stronger opioid Morphine	0.3 mg/kg po q3–4h 0.1 mg/kg IM or SC q3–4h 0.1 mg/kg IV q2h 0.05–0.06 mg/kg/hr IV cont. Infusion
	Morphine controlled release	1 mg/kg po q12h
	Methadone	0.1 mg/kg IV or po q4h initially for 2–3 doses, then q6–12h (titrate carefully)

<sup>a</sup> Assess pain relief/If not relieved, go to moderate pain/consider adjuvant/monitor and treat side effects.

<sup>b</sup> Assess pain relief/If not relieved, go to severe pain/consider adjuvant/monitor and treat side effects.

#### *How to Assess Treatment Failure and When to Change Therapy*

The success of pain treatment can only be determined if pain severity is monitored regularly and consistently, preferably by the self-reporting child, using measures such as faces scales or visual analogue scales. Analgesic failure may be attributable to poor compliance, poor drug absorption, inadequate drug dose or dosing frequency, inappropriate drug selection, or a change in the status of the underlying pathologic condition(s) causing the pain. In general, the indication for an opioid switch is dose-limiting toxicity rather than inadequate analgesia. When analgesia appears to be inadequate, the common explanations noted above should be considered.

#### *How to Increase the Dose of Opioids and Calculate “Rescue” Doses*

Rescues are supplemental doses of opioid administered as needed to allow a patient to enjoy additional needed analgesia. Rescue doses of opioid may be calculated as approximately 5% to 10% of the total daily opioid requirement and may be administered every hour.<sup>259</sup> Incremental opioid dosage adjustments can be calculated as follows:

1. If greater than approximately six rescue doses of opioid are given within a 24-hour period, then the total daily dose should be increased by the total quantity of required rescue medication. Alternatively, the baseline opioid dose may be increased empirically by 50%.<sup>259</sup>
2. Rescue doses are calculated as a proportion of the baseline opioid dose. As noted, this dose can be 5% to 10% of the total daily dose. An alternative guideline for opioid infusions is between 50% to 200% of the hourly basal infusion rate.<sup>259</sup>

#### *When and How to Change to an Alternative Opioid*

The usual indication for changing an opioid is dose-limiting toxicity. After a prolonged period of regular dosing with one opioid, equivalent analgesia may be attained with a dose of a second opioid that is smaller than that calculated from an equianalgesic

table.<sup>259</sup> The opioid change is usually accompanied by a reduction in the equianalgesic dose (~50% for short half-life opioids). This dose reduction may be less if the change is made in the setting of inadequate pain control; it may be more in the medically fragile and those with severe opioid toxicity. In contrast, the dose of methadone required for equivalent analgesia after changing may be of the order of 10% to 20% of the equianalgesic dose of the previously used short half-life opioid.<sup>260</sup>

#### *The Treatment of Opioid Side Effects*

All opioids can potentially cause the same constellation of side effects (constipation, nausea, vomiting, neuropsychological sequelae), and children should be asked about these potential problems. Other than constipation, tolerance to many opioid side effects often develops within the first week of commencing opioids. Concurrent treatment with a stool softener and a stool stimulant should be considered in patients with opioid-induced constipation. The use of dextroamphetamine and methylphenidate as treatments for opioid-induced somnolence in children has been reported.<sup>261</sup> A switch to an alternative opioid may be considered in patients with opioid-induced side effects refractory to treatment.

#### *When to Use Adjuvant Analgesics*

Adjuvant analgesics are a heterogeneous group of drugs that have a primary indication other than pain management but are analgesic in some painful conditions.<sup>262</sup> They are commonly prescribed with primary analgesic drugs. Common classes of adjuvant analgesics include antidepressants, anticonvulsants, neuroleptics, psychostimulants, antihistamines, corticosteroids, and centrally acting skeletal muscle relaxants and associated drugs. For children with HIV infection, the tricyclic antidepressants may have a useful role in the treatment of painful peripheral neuropathy and pain associated with herpes zoster.<sup>263</sup> Guidelines for the choice and management of antidepressants as adjuvant analgesics in children have been outlined.<sup>264</sup> Data regarding the use of

other adjuvant analgesics in pediatric pain management are evolving.

#### *The Management of Painful Procedures*

There is a wide array of available means of preventing pain during potentially painful procedures in children (ranging from nonpharmacologic methods to general anesthesia). Individual practitioners and institutions must develop their own protocols for the safe administration of sedative agents for the management of painful procedures in children. The eutectic mixture of local anesthetics (EMLA) has become a useful method of topical anesthesia before venipuncture or lumbar puncture.<sup>265, 266</sup> The depth of penetration of the anesthesia afforded by EMLA increases in proportion to the duration of application.<sup>267</sup>

#### Summary

Table 19 provides a summary of the major issues raised in this discussion of palliative care and pain management in infants, children, and adolescents with HIV infection. Appropriate attention to palliative care and pain management has a profound and direct impact on quality of life and should be part of the overall management plan for all children with HIV infection.

#### CONCLUSION

The Working Group has attempted to provide a succinct summary of relevant background information and authoritative guidance regarding the currently appropriate use of antiretroviral agents and management of the common complications of HIV infection pertinent to the care of infants, children, and adolescents with HIV/AIDS. This supplement does not reiterate the principles of therapy of HIV infection nor the guidelines for the use of antiretroviral agents in adults and adolescents infected with HIV, which have been delineated and recently published elsewhere.<sup>5,6</sup> It does contain a reprinting of recently updated recommendations for preventing OI.<sup>10</sup> Adults, adolescents, and children with HIV infection share many common features with respect to disease pathogenesis, complications (including drug-related toxicities), and common principles of management. However, there are distinguishing features

unique to children and younger adolescents with HIV infection (including natural history, drug metabolism, and physiologic and emotional development) that were not addressed specifically in the adult HIV treatment guidelines. Regrettably, clinical trials of antiretroviral agents and drugs for the treatment/prevention of OI in children have often lagged behind studies in adults or have been entirely lacking, and development of drug formulations appropriate for children has been inadequate. These delays and the paucity of pediatric-specific data notwithstanding, the development and promulgation of rational and reasonable pediatric treatment guidelines while studies in children are planned or are in progress cannot be deferred any longer.

To maximize therapeutic options for pediatric patients with HIV infection, all FDA-approved antiretroviral and OI therapies should be made available for children despite the fact that some may lack specific pediatric indications. Additionally, the conduct of clinical trials to define the pharmacokinetics, safety, and effectiveness of new antiretroviral and antimicrobial agents in infants and children should be a high priority for the FDA and the pharmaceutical industry. Studies of new drugs should be conducted in children simultaneously with or soon after initiation or completion of studies in adults.

In addition to providing specific recommendations regarding the appropriate use of antiretroviral therapies that slow the reproduction of HIV, help restore immune function, reduce complications, and prolong survival, these guidelines also discuss the critically important issues of neurodevelopment, nutrition, and palliation of pain as they apply to the evaluation and management of HIV infection in infants, children, and adolescents. Attention to such supportive care issues in providing comprehensive management of infants, children, and adolescents with HIV infection will improve the quality of their lives by promoting optimal growth and development and the alleviation of suffering and pain.

These guidelines will require frequent revisions as new information is accrued from clinical trials and experience.

#### APPENDIX

##### PACTG Protocols Cited in Guidelines

PACTG 076 is a completed, phase III, randomized, placebo-controlled trial that demonstrated the safety and efficacy of a ZDV regimen for the prevention of perinatal HIV infection. The 076 regimen consists of ZDV (100 mg, po, 5 times/day) given to pregnant women of >14 weeks to <34 weeks gestation, intravenous ZDV during labor and delivery (loading dose of 2 mg/kg, followed by 1 mg/kg/h), and oral ZDV syrup (2 mg/kg qid) given to their infants for six weeks.

PACTG 128 is a completed, randomized, blinded clinical trial that compared the safety and tolerance of two doses of ZDV (180mg/m<sup>2</sup> vs 90 mg/m<sup>2</sup>) in mildly to moderately symptomatic HIV infected children 3 months to 12 years of age.

PACTG 138 is a completed, open-label clinical trial that compared the safety and tolerance of two doses of 2',3' dideoxycytidine (ddC), (0.005 mg/kg vs 0.01 mg/kg q8h) in children 3 months to 18 years of age with symptomatic HIV infection who had ZDV intolerance, signs of disease progression after 6 months of ZDV therapy, or both.

PACTG 144 is a completed, randomized, blinded clinical trial that compared the efficacy (based on disease progression and

**TABLE 19.** Pediatric Pain Management: Summary of General Principles

- Opioids can be used safely for infants and children
- Take a preventive approach—use round-the-clock rather than PRN dosing
- Individualize therapy
- Avoid intramuscular or subcutaneous routes of administration of pain medications when possible
- Monitor and treat side effects of analgesics
- Be aware of various signs of pain and methods of their assessment to assess and manage pain regularly
- Consult pain management team when available
- Use behavioral techniques and local anesthesia such as EMLA for all painful medical procedures whenever possible
- Consider and address child's families' beliefs and concerns regarding pain, use of pain medications, and use of behavioral techniques in developing pain management therapy

survival) of 2 doses of ddI (50 mg/m<sup>2</sup> q12h vs 150 mg/m<sup>2</sup> q12h) in children 3 months to 18 years of age with symptomatic HIV infection who had ZDV intolerance, signs of disease progression after 6 months of ZDV therapy, or both.

PACTG 152 is a completed, randomized, blinded clinical trial that compared the safety and efficacy of ZDV monotherapy (180 mg/m<sup>2</sup> q6h) to ddI monotherapy (120 mg/m<sup>2</sup> q12h) and to combination therapy with ZDV (120 mg/m<sup>2</sup> q6h) plus ddI (120 mg/m<sup>2</sup> q12h) in children 3 months to 17 years of age with symptomatic HIV infection.

PACTG 247 is an ongoing, randomized, double-blind, controlled study to determine whether caloric supplementation started within the first 14 days of life results in improved growth in HIV-infected infants during the first year of life by comparing growth achieved by infants consuming fortified infant formula (containing 25.7 kcal/oz) with that seen in infants receiving standard formula (20 kcal/oz).

PACTG 300 is a completed, randomized, blinded clinical trial that compared combination therapy with ZDV (160 mg/m<sup>2</sup> tid) plus 3TC (4 mg/kg q12h) to the better of ddI monotherapy (120 mg/m<sup>2</sup> q12h) vs ZDV (160 mg/m<sup>2</sup> tid) plus ddI (90 mg/m<sup>2</sup> q12h) in children 42 days to 15 years of age with symptomatic HIV infection.

PACTG 331 is an ongoing, open-label study of the safety, tolerance, and pharmacokinetics of ZDV in HIV-exposed premature infants  $\leq$ 34 weeks' gestation. Initial ZDV dosing is 1.5 mg/kg every 12 hours (intravenously or orally), with a dosage increase to 2 mg/kg every 8 hours at 12 to 16 days of age. Other dosing modifications are made based on the results of an infant's pharmacokinetic studies.

PACTG 338 is an ongoing, open label, randomized trial of novel antiretroviral therapy in HIV-infected children 24 months to 17 years of age treated continuously with the same antiretroviral therapy for at least 16 weeks. Subjects are clinically and immunologically stable, maintaining CDC immunologic classification of 1 or 2 for the 4 months before entering the study and having not experienced a new category C diagnosis during the previous year. This study compares the following treatments for safety and efficacy in reducing HIV plasma RNA: ZDV (160 mg/m<sup>2</sup> tid) + 3TC (4mg/kg q12h) versus d4T (1 mg/kg q12h, 30 mg/kg q12h if >30 kg and <60 kg; 40 mg q 12 h if >60 kg) + Ritonavir (350 mg/m<sup>2</sup> q12h) versus ZDV (160 mg/m<sup>2</sup> tid) + 3TC (4mg/kg q12h) + Ritonavir (350 mg/m<sup>2</sup> q12h). Based on results of the 12-week interim analysis showing that the combination of ZDV + 3TC was less effective in decreasing HIV plasma RNA than either of the ritonavir-containing regimens, the ZDV + 3TC arm was stopped. The protocol was revised by adding an additional treatment arm to provide a treatment option for those children on the ZDV + 3TC arm who had HIV plasma RNA levels of  $\geq$ 10 000 copies/mL after at least 12 weeks of therapy: d4T (1 mg/kg q12h, 30 mg/kg q12h if >30 kg and <60 kg, 40 mg q 12 h if >60 kg) + Nevirapine (120 mg/m<sup>2</sup> qd  $\times$  14 days then bid) + Ritonavir (350 mg/m<sup>2</sup> q12h).

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# 1997 USPHS/IDSA REPORT ON THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

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**Antiretroviral Therapy and Medical Management of Pediatric HIV Infection**  
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