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Pediatric Human Immunodeficiency Virus Infection

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MAGNITUDE OF THE PROBLEM WORLDWIDE

The World Health Organization estimates that more than 13 million people worldwide are infected with human immunodeficiency virus type 1 (HIV-1). Of these individuals, 4 million are women and 1 million are infants and children; most of the infants and children were vertically infected with HIV (50, 176). Eighty percent of the infected women and children reside in sub-Saharan Africa, where the estimated prevalence of HIV-1 infection is 2,500/100,000 women in the 15- to 49-year age group. In such areas of the world, pediatric AIDS cases may make up as much as 15 to 20% of total AIDS cases. In developed countries, pediatric AIDS cases represent only a small percentage of the total (190).

It is estimated that by the year 2000, the cumulative number of HIV-infected adults and children will rise to 30 to 40 million and the HIV pandemic will be responsible for the deaths of 3 million women and more than 2.5 million children worldwide (50). An additional 5.5 million children may be orphaned because of the premature HIV-associated death of their parents, further magnifying the problem of HIV for the pediatric population.

The number of HIV-infected women of childbearing age is increasing. Their infants are exposed to HIV in utero or at the time of delivery, thereby increasing the numbers of HIV-infected children. It has been proposed, by using a mathematical model, that when maternal infection rates reach 2 to 3%, HIV infection acquired by the perinatal route could become the most common cause of death in children (14).

MAGNITUDE OF THE PROBLEM IN THE UNITED STATES

Since the first report of an infant with AIDS in November 1982 (199), the incidence of HIV-1 infection in the pediatric population has increased exponentially. In the United States, 71,818 cases of AIDS in women have been reported to the Centers for Disease Control and Prevention (CDC) through December 1995 (46). During the same period, 6,948 cases of pediatric AIDS were reported (46), most of which resulted from vertical transmission of HIV from infected mothers. Overall, women constitute 12% of adult and adolescent AIDS patient in the United States. The predominant mode of transmission for these women in past years has been the sharing of needles during parenteral use of illicit drugs. This mode of transmission continues to be problematic; however, heterosexual transmission is currently the most common source of infection for mothers of vertically infected children in the United States (176). The partners of these women are often infected with HIV as a result of sharing needles, and they transmit the virus to the women by sexual contact. This trend is particularly true in the southern United States, where more heterosexually acquired AIDS cases are reported than in any other region of the country (37).

It should be recognized that the number of reported AIDS cases grossly underestimates the true magnitude of the problem. Since 1988, the CDC has coordinated blinded HIV serosurveys in various clinical settings (75), the largest being the national survey of childbearing women. Transfer of maternal antibodies to the fetus during pregnancy results in virtually all infants born to seropositive HIV-infected mothers being HIV seropositive at birth. This type of serosurvey therefore monitors the prevalence of maternal HIV antibody, even though it is conducted through blinded HIV testing of newborn blood samples. Such HIV serosurveys are under way in 44 states, Puerto Rico, and the District of Columbia. Numbers derived from these studies suggest that more than 7,000 HIV-infected women deliver infants each year. The true number of infected children in the United States therefore probably exceeds 20,000 (75, 100).

Prevalence and Incidence of HIV Infection in Women and Infants

AIDS surveillance data have been useful in tracking the severe end of the HIV disease spectrum, however, HIV seropositivity studies give a more accurate view of the current situation and provide a better estimate of the severity of the problem to come. Seroprevalence studies done on newborn cord blood samples demonstrate that seroprevalence varies widely both between and within states (109). The highest seroprevalence rates have been seen in Washington, D.C. (0.9%), New York (0.61% in New York City, and 0.16% in upstate New York), New Jersey (0.55%), and Florida (0.54%). Most other states have rates below 0.1%. The overall national rate reported in 1993 was 0.17%, corresponding to over 7,000 HIV-infected women delivering live infants each year (110). Many of these women go unidentified during their pregnancies, and many of their infants are not recognized as being at high risk for vertically acquired HIV infection. Most states that have conducted these seroprevalence surveys over multiple years have shown a stable prevalence rate, however some states, particularly those to the south, show a troublesome increase (37).

The impact of HIV on Hispanic and African American children living in urban areas is particularly striking. Overall, 59% of perinatally acquired AIDS cases in the United States are among African American children and 26% are among Hispanics (176). Although the largest number of pediatric AIDS deaths occur in the first year of life, the relative impact of AIDS as a cause of death has been most dramatic in the 1- to 4-year-old group. In New York City, HIV-related illness is the leading cause of death among Hispanic children and the second leading cause of death (after unintentional injury) among African American children in the 1- to 4-year-old age group (175).

ROUTES OF HIV ACQUISITION IN THE PEDIATRIC POPULATION

Of the reported children younger than 13 years old with AIDS in the United States, 90% were born to mothers with HIV infection or HIV risk factors, 5% received blood transfusions or tissue transplants, 3% were hemophiliacs, and 1% had no identified risk factor (46). Some children have also become HIV infected through being victims of sexual abuse (104, 108). The primary focus of this review will be on vertically acquired HIV infection. Other routes of infection in this age group are summarized first.

HIV Acquisition from Blood and Tissue Products

The first cases of hemophilia-associated AIDS were recognized in 1982 (30). Concerns regarding a transfusion-acquired

infectious agent increased later that year when an infant developed unexplained immunodeficiency after transfusion of platelets derived from a donor who subsequently developed AIDS (3). When nationwide screening of blood products was implemented in the spring of 1985, 0.04% of donated blood and blood products were found to be HIV seropositive (211). The same year, most hemophiliacs who had received clotting-factor concentrate were found to be HIV seropositive (94). By the end of 1992, more than 2,000 cases of AIDS had been reported in persons with hemophilia, accounting for 1% of cases in adults and children. Of the 6,948 cases of AIDS reported to date in children, 227 (3%) were in hemophiliacs who had received clotting factor concentrate and 366 (5%) were in children who had received other transfusions or tissues (46).

Sexual Transmission of HIV in the Pediatric Age Group

The adolescent population represents a group of individuals at high risk for acquiring HIV infection via the sexual route. The present distribution of reported cases of AIDS in this age group indicates that the largest category includes adolescents who acquired HIV infection from blood products to correct coagulation defects (30%). The second largest single category includes males who have sex with males (25%), followed by 13% who acquired the infection via the heterosexual route. Acquisition of HIV via the sexual route in adolescents therefore accounts for 38% of the cases in this group. As in adults, adolescents who use injected drugs also make up a substantial percentage of the total (41, 46). Heterosexual transmission of HIV is on the rise, representing a further risk to sexually active adolescents. An in-depth discussion about the growing problems associated with HIV and the adolescent population is beyond the scope of this review but can be found elsewhere (5).

Sexual abuse is another route whereby children can become infected with HIV (104, 108). Although only a few cases have been documented, this problem compounds the already overburdened medical and psychosocial evaluation of these patients.

Household Transmission of HIV

Only eight reported cases of household transmission of HIV not associated with sexual contact, intravenous drug use, or breast-feeding have been published, making this route of transmission plausible but exceptionally rare (32, 38, 40, 43, 99, 106, 248). Of the eight reported cases, five had documented or probable blood contact. The route of transmission for the others is not clear. Persons who provide health care in household settings should be instructed on appropriate infection control techniques.

TRANSMISSION OF HIV FROM MOTHER TO INFANT

Transmission of HIV from mother to infant is not absolute but is relatively efficient. Prospective studies have reported mother-to-infant HIV transmission in 13 to 39% of infants born to HIV-infected women. Published estimates range from 13 to 20% in Europe, 25 to 30% in Africa, and 16 to 39% in the United States (92, 103, 193). These studies have used different definitions and laboratory assessments of infection with various lengths of pediatric follow-up. Loss to follow-up and high infant mortality can have a substantial effect on the accuracy of these estimates.

Risk Factors for Vertical Transmission

Many characteristics of the HIV-infected mother may be associated with increased risk of perinatal HIV transmission. These different characteristics may indeed explain the variations in the transmissibility of HIV in different cohorts of HIV-infected women. Studies demonstrating lower transmission rates have included predominantly asymptomatic pregnant mothers. In comparison, women with symptomatic HIV infection or AIDS may have an increased risk of transmitting HIV to their infants (15). Perinatal transmission may be affected by the mother's disease status, the route of delivery, the duration of membrane rupture, the presence of obstetrical complications such as maternal hemorrhage or infection, and perinatal feeding practices (92, 103, 121, 175). Maternal disease status can be measured by using clinical criteria, immunologic criteria, or both. Advanced maternal HIV disease (15), low $CD4^+$ cell count, high viral load as determined by p24 antigenemia (91) or viral titers (141), and the syncytium-inducing phenotype of the maternal virus (219b) may be associated with increased risk of mother-to-infant HIV transmission. Several studies suggest that the virus-neutralizing ability and amount of certain maternal antibodies that bind gp120 or gp160 (HIV envelope glycoproteins) might alter the risk of transmission (72, 105, 203), but no consistent pattern has emerged (112, 179, 195, 210).

Higher rates of transmission have been reported for infants delivered vaginally than for those delivered by cesarean section in some studies (92, 103, 121); however, the differences have been only marginally significant.

The presence of other sexually transmitted diseases during pregnancy, particularly active syphilis, appears to increase the likelihood of HIV transmission, possibly because of placentitis due to *Treponema pallidum* (188). Other ulcerative genital infections may also increase transmission rates.

Perinatal feeding practices can also affect vertical HIV transmission, as HIV has been conclusively documented to occur via breast-feeding (232). Transmission via the breast milk may be influenced by the type of milk ingested (colostrum versus later milk), duration of breast-feeding, and maternal factors such as duration of the mother's HIV infection, her viral load, and the antibody content of her milk (67, 177, 246).

It is becoming clear that rather than thinking in terms of overall mother-to-infant HIV transmission rates and therefore transmission risks, it is exceedingly important to consider maternal characteristics that may increase or decrease the risk of transmission. As these factors become identified, they become potential targets for intervention.

Timing of Vertically Transmitted HIV Infection

Perinatal transmission of HIV may occur before, during, or after birth, but the relative importance of each of these routes is not well defined. Recently, experts suggested a working definition of intrauterine infection as a positive PCR or HIV culture or p24 antigen test on the infant's blood between birth and 48 h of life. Perinatal infection is defined as negative assays shortly after birth with positive results occurring later (22). Failed attempts to routinely isolate HIV or to detect it by PCR just after birth support the view that many infants acquire infection at or very near the time of birth (82). There is also evidence that intrauterine infection does occur on the basis of examination of placentas and fetal tissue following pregnancy termination, but estimates of its frequency have differed (76). Use of the proposed definition to distinguish intrauterine from perinatal infection may help identify independent risk factors for these two modes of transmission.

Postnatal vertical transmission of infection through breast-feeding can occur, both in children whose mothers were infected after giving birth and in children born to women with established HIV infection (80, 258). Rates of transmission via breast-feeding have been estimated as 29% when the mother is acutely infected and 14% when the mother is chronically infected (80), but individual estimates from small cohorts vary widely. In developed areas of the world, where there are safe alternatives to breast-feeding, HIV-infected women are advised not to breast-feed (31). In areas of the world that have a high incidence of malnutrition and mortality due to diarrheal illness, the benefits associated with breast-feeding may outweigh the potential for HIV transmission. Decision analyses have evaluated the risk of mortality associated with not breast-feeding compared with the risk of transmission of HIV through breast milk (117, 258). The results support the current World Health Organization and CDC recommendation in favor of breast-feeding for HIV-infected mothers in many developing parts of the world. Two randomized, prospective trials of breast-feeding versus bottle feeding are planned in Africa in an attempt to determine the true rate of breast-feeding transmission so that more informed public health advice can be given.

Strategies To Interrupt Vertical Transmission

Despite obstetrical initiatives to encourage voluntary HIV testing during pregnancy, many infected women go undiagnosed. Once an HIV-infected pregnant woman is recognized, a number of interventions have been proposed that may decrease the rate of perinatal HIV transmission. Some of these interventions are being evaluated by the National Institutes of Health through the AIDS Clinical Trials Group (ACTG). Strategies being used include decreasing the HIV load of the infected pregnant woman by antiretroviral therapies, maintaining placental integrity by early treatment or prophylaxis of genital tract infections, providing passive HIV antibody to the pregnant woman, fetus, and newborn, and providing active or passive enhancement of fetal and neonatal anti-HIV specific immunity. Each of these strategies is discussed in some detail below.

Maternal antiretrovirus therapy. The most encouraging advances in blocking mother-to-infant HIV transmission are the results of ACTG 076 (62). This study was designed to assess the protective effect of zidovudine (ZDV) in the prevention of vertical transmission of HIV from mother to infant. The pregnant women had not received previous antiretroviral therapy, and their $CD4^+$ cell counts were greater than 200 cells per μl on enrollment. The women were randomized to receive oral ZDV or placebo during the second or third trimester of pregnancy and then given the same study drug intravenously at the time of delivery. Infants were given the same study medication orally for the first 6 weeks of life. Interim study analysis done in February 1994 showed a decrease in the rate of mother-to-infant transmission in the ZDV-treated group. Of the infants whose mothers were treated with placebo, 25% were eventually found to be infected, while only 8% of the infants in the treatment arm of the study were infected. This corresponded to a 67.5% relative reduction in transmission risk. The trial was halted, and all patients were offered open-label ZDV (62). While this treatment offers an unprecedented advance in the potential control of pediatric HIV infection, HIV can clearly still be transmitted despite ZDV therapy of the mother. Efforts to further reduce this risk must continue. One worrisome caveat is that transmission of ZDV-resistant virus has been reported in children born to mothers treated with ZDV (194). Interventions for women who have previously taken ZDV or other antiretroviral therapy, and for women with $CD4^+$ cell counts less than 200 cells per μl need to be further explored.

The recent development of nonnucleoside reverse transcriptase inhibitors, which have high affinity for HIV reverse transcriptase and induce a rapid and marked decline in p24 antigen levels (49, 113, 133, 142), has led to the suggestion that these drugs may be helpful in reducing perinatal HIV transmission, particularly if used in combination with other strategies.

Maternal and infant HIV immunotherapy. AIDS vaccine immunotherapy trials are also under way to assess the effect of vaccines on vertical transmission. These studies are based on the finding that cell-mediated immune responses appear to correlate with a stable clinical course in HIV-infected patients (216). An AIDS vaccine that boosts cell-mediated immunity and broadens the neutralizing-antibody repertoire may reduce vertical transmission of HIV (241). A variety of products for passive immunization are being contemplated (72, 123, 129, 263). Passive immunotherapies have been used with variable success for other infections, including varicella and hepatitis B. It is hoped that an approach similar to that taken to prevent these infections can be implemented for the prevention of HIV.

Trials have been designed for the United States and Uganda to test HIV immunoglobulin (HIVIG) in an intravenous formulation that is prepared from the plasma of HIV-infected donors (61, 220). A phase III U.S. trial, begun in October 1993, is enrolling pregnant women already receiving ZDV. Monthly infusions of HIVIG are given to the mother during late pregnancy, and the infant receives a single dose shortly after birth. In the Ugandan trial, one infusion is given to the mother and one is given to the infant. Preliminary results of these trials are not yet available.

An alternative to HIVIG prepared from infected donors includes polyclonal antibodies prepared from the plasma of uninfected donors who have been immunized with experimental or (eventually) licensed HIV vaccines. This product would probably be easier to produce and standardize and would be more readily accepted by patients than products prepared from HIV-infected individuals.

Cell-mediated immune responses to highly conserved parts of the virus have been found in both HIV-infected individuals and others who appear to have been exposed to the virus without becoming infected (55). This finding suggests that some degree of protective immunity could occur via cell-mediated mechanisms. Both humoral and cell-mediated responses can be induced by active immunization of the mother and/or infant (84). Active immunization is an attractive approach because of the potential for long-term immunity (148). Immunogens tested in uninfected human volunteers have included recombinant preparations of HIV-1 envelope glycoprotein, synthetic peptides, and noninfectious virus-like particles (96). None of these candidate immunogens have elicited impressive immune responses in animal models, nor have they elicited detectable $CD8^+$ cytotoxic activity. Nevertheless, phase I trials in which pregnant HIV-infected women or their infants are immunized with recombinant envelope vaccines have been initiated (58). Clearly, further evaluation is necessary to determine the extent to which these vaccines are appropriate for movement into large-scale efficacy trials.

In addition to being used as a strategy to interrupt vertical HIV transmission, immunotherapy is being evaluated as a potential immunomodulator in children with known HIV infection (61, 129, 230). One randomized double-blind phase I/II trial of active immunization of infants and children against HIV has been completed, but data are not yet available.

Early identification of HIV-infected pregnant women. Early identification of HIV-infected pregnant women is critical if any of the strategies to prevent vertical transmission are to succeed. The current failure to uniformly offer HIV-related counseling and testing reflects the heterogeneity and inadequacies of our current health care system. Offering HIV testing to all woman during pregnancy can result in a high rate of acceptance (9). Ideally, the need for counseling and testing of all pregnant women should be recognized by all health care providers. This does not occur and is unlikely to be accomplished voluntarily despite the results of ACTG 076, demonstrating that ZDV can interrupt transmission. If it were possible to identify all pregnant HIV-infected women and administer ZDV to them, the number of anticipated infected infants could be dramatically reduced (79, 254). The American Academy of Pediatrics (237) and a consensus statement from the HIV Resource Center (115) have made the recommendation that HIV counseling and HIV testing be routinely offered by all health care providers to women of reproductive age. The offer of HIV antibody testing should be made as early as possible during the prenatal period, and if women are not tested during pregnancy, counseling and testing should be offered during the postnatal period (45).

Because of the apparent failure of the health care system to identify the majority of HIV-infected pregnant women, some experts have proposed mandated HIV testing of all pregnant women (254). This proposal has elicited considerable controversy involving rights of privacy (196). Some experts are convinced that mandated testing would result in the failure of some women to seek any prenatal care. Perhaps a mandated active (signed) refusal for testing would be a more appropriate strategy that would ensure some counseling while preserving rights to privacy (45, 196, 254). Despite these potentially volatile issues, it remains clear that HIV counseling and voluntary antenatal testing offer opportunities to identify HIV-infected women, begin therapy, and potentially prevent HIV infection in their children. The adverse consequences of the diagnosis, including stress and the possible stigma and discrimination against the woman and her family, should be understood (182).

DEFINING HIV INFECTION IN CHILDREN LESS THAN 13 YEARS OF AGE

In 1987, the CDC developed a staging system for HIV-exposed and HIV-infected infants (33). The recently published 1994 revised classification system for HIV infection in children less than 13 years of age replaced the 1987 classification system and was deemed necessary as further information about the natural history of the disease became available (42). In the most recent system, HIV-infected children are classified into mutually exclusive categories according to their infection status, their clinical status, and their immunologic status. These categories will be reviewed in some detail, with special attention given to the diagnostic challenge of children born to HIV-infected women.

Diagnostic Challenge of a Child Born to an HIV-Infected Mother

Diagnosis of HIV infection in children born to HIV-infected mothers is complicated by the presence, in almost all cases, of maternal anti-HIV antibody, which crosses the placenta to the fetus. Overall, less than one-third of these children are actually infected (92, 103, 219a). HIV antibody assays including enzyme immunoassay and Western immunoblotting detect primarily immunoglobulin G (IgG) antibodies with a very high degree of sensitivity. In adults, a positive enzyme immunoassay confirmed by immunoblotting is very highly specific for HIV infection (36, 114, 229). In uninfected children, the maternal antibody usually disappears by 9 months of age but occasionally persists until 18 months (92). It is for this reason that conventional HIV antibody tests cannot be used to reliably predict the infection status in children under 18 months of age (223).

Despite these problems, HIV infection can be reliably diagnosed in the first year of life by other methods of testing. PCR and virus culture have proven to be the most sensitive and specific assays for this purpose (16, 182). The use of these assays can identify up to 50% of infected infants at birth and nearly 100% of infected infants by 3 to 6 months of age (28, 71, 185, 192, 219a, 240). It should be recognized that false-positive PCR results do occur during the first week of life (198). The standard p24 antigen assay is less sensitive than either virus culture or PCR, especially when anti-HIV antibody levels are high, because it fails to detect immunocomplexed p24 antigen (197). Modifications of this standard assay that allow acid dissociation of immune complexes have improved its sensitivity in the infant population; however, the sensitivity remains considerably lower than that of PCR and culture (23). Samples taken in the first week of life have been somewhat problematic, resulting in false-positive and false-negative tests (144, 166, 178).

To circumvent the presence of confounding maternal antibodies, two additional methods for detecting infant-specific HIV antibodies have been evaluated. These are in vitro production of virus-specific antibodies by the patient's lymphocytes (1) and detection of patient-specific IgA antibodies to HIV (IgA does not cross the placenta) (143, 191, 250). Although these methods are potentially useful, they have not been included in algorithms for determining infection status because of their limited availability and their decreased sensitivity when compared with PCR and viral culture. Currently, HIV culture and PCR for the identification of HIV-specific nucleotide sequences are the methods of choice for detecting virus in peripheral blood (135). In laboratories with experienced personnel, both of these assays appear to be highly sensitive and specific, making early diagnosis possible (8, 28, 71, 185, 192, 219a, 240).

Because of the difficult issues regarding testing and establishing a diagnosis of HIV infection in early infancy, the present criteria set forth by the CDC for the diagnosis of HIV infection in childhood are age dependent (Table 1) (42). For children older than 18 months, standard serologic testing is used because maternal antibody has largely disappeared by this time. For asymptomatic infants younger than 18 months, two positive results of HIV culture, PCR, or p24 antigen assay are needed to make the diagnosis of HIV infection, although a single positive result is regarded as highly suspicious. To ensure that late seroreverters are not missed, it is recommended that repeat antibody testing be done at 24 months of age. If the antibody test remains negative at this time, the child is almost certainly not infected (42).

Children born to mothers with HIV infection are defined as seroreverters and considered uninfected with HIV if they become antibody negative after 6 months of age, have no other laboratory evidence of HIV infection, and have not met the AIDS surveillance case definition criteria (42).

Immunologic Categories for HIV-Infected Children

The most notable laboratory finding in HIV-infected children, particularly as the disease progresses, is a gradual loss of

TABLE 1. Diagnosis of HIV infection in children

Diagnosis	Description[a]
HIV infected	(i) A child <18 months of age who is known to be HIV seropositive or born to an HIV-infected mother and has positive results on two separate determinations (excluding cord blood) from one or more of the following HIV detection tests HIV culture HIV PCR HIV antigen or meets criteria for AIDS diagnosis based on the 1987 AIDS surveillance case definition (ii) A child ≥18 months of age born to an HIV-infected mother or any child infected by blood, blood products, or other known modes of transmission (e.g., sexual contact) who is HIV antibody positive by repeatedly reactive EIA and confirmatory test (e.g., Western blot or IFA) or meets any of the criteria in (i) above.
Perinatally exposed	A child who does not meet the criteria above who is HIV seropositive by EIA and confirmatory test (e.g., Western blot or IFA) and is <18 months of age at the time of testing or has unknown antibody status but was born to a mother known to be infected with HIV
Seroreverter	A child who is born to an HIV-infected mother and who has been documented as HIV antibody negative (i.e., two or more negative EIA performed at 6–18 months of age or one negative EIA after 18 months of age) and has had no other laboratory evidence of infection (has not had two positive viral detection tests, if performed) and has not had an AIDS-defining condition.

[a] EIA, enzyme immunoassay; IFA, immunofluorescence assay.

T-lymphocyte immunity. Initially, the peripheral blood lymphocyte count can be normal, but lymphopenia eventually develops because of a decrease in the total number of circulating T cells. The cells most greatly affected are the helper T ($CD4^+$) lymphocytes. Suppresser T ($CD8^+$) lymphocytes often increase in number initially and become depleted late in the course of infection. These changes in cell populations result in a decreased CD4-to-CD8 cell ratio. The normal values for peripheral $CD4^+$ lymphocyte counts and percentages are age dependent, starting quite high and reaching adult-like normal levels by the age of 6 years (70, 88, 193). It is imperative that physicians caring for young children infected with HIV recognize this fact, because a normal $CD4^+$ cell count for an adult may be considered drastically low during infancy.

Functional defects of T cells are seen regularly. At the extreme, the response of T lymphocytes to plant lectin mitogens (phytohemagglutinin, concanavalin A, and pokeweed) is decreased or absent and patients become anergic to skin test antigens such as candida, trichophyton, and tuberculin antigens (97, 151). B-lymphocyte counts remain normal or increased in number. Ig concentrations in serum, particularly IgG and IgA concentrations, are frequently elevated, resulting

TABLE 2. Immunologic categories based on age-specific $CD4^+$ lymphocyte counts and percentage of total lymphocytes

Immunologic category	Lymphocyte counts in children aged:					
	<12 mo		1–5 yr		6–12 yr	
	No. of $CD4^+$ cells/μl	% Lymphocytes	No. of $CD4^+$ cells/μl	% Lymphocytes	No. of $CD4^+$ cells/μl	% Lymphocytes
No evidence of suppression	≥1,500	≥25	≥1,000	≥25	≥500	≥25
Evidence of moderate suppression	750–1,499	15–24	500–999	15–24	200–499	15–24
Severe suppression	<750	<15	<500	<15	<200	<15

TABLE 3. Clinical categories for children with HIV infection

Category	Description
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.
A (mildly symptomatic)	Children with two or more of the conditions listed below but none of the conditions listed in categories B and C Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site) Hepatomegaly Splenomegaly Dermatitis Parotitis Recurrent or persistent upper respiratory infection, sinusitis, or otitis media
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 this category include but are not limited to Anemia (<8 g/dl), neutropenia (<1,000/mm^3), or thrombocytopenia (<100,000/mm^3) persisting ≥30 days Bacterial meningitis, pneumonia, or sepsis Candidiasis, oropharyngeal (thrush), persisting for >2 months in children >6 months of age Cardiomyopathy Cytomegalovirus infection, with onset before 1 month of age Diarrhea, recurrent or chronic Hepatitis HSV stomatitis, recurrent (more than two episodes within 1 year) HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome Leiomyosarcoma LIP or pulmonary lymphoid hyperplasia Nephropathy Nocardiosis Persistent fever (lasting more than 1 month) Toxoplasmosis, onset before 1 month of age Varicella, disseminated
C (severely symptomatic)	Children who have any condition listed in the 1987 surveillence case definition for AIDS, with the exception of LIP (see Table 4)

in polyclonal hypergammaglobulinemia (54, 68, 200). Less commonly, panhypogammaglobulinemia is seen (158). Specific antibody responses to antigen to which a patient has not previously been exposed can be blunted or absent, a particular concern when administering childhood vaccinations (20). Patients with dysgammaglobulinemia may benefit from the regular administration of pooled intravenous Ig.

Three mutually exclusive immunologic categories have been defined to categorize children by the severity of their immunosuppression; no suppression, moderate suppression, and severe suppression (Table 2) (42). Several findings complicate the use of $CD4^+$ counts for assessing immunosuppression resulting from HIV infection in children. Normal $CD4^+$ counts are higher in children than in adults, and the normal range declines gradually over the first few years of life (70, 88). Children may also develop opportunistic infections at higher $CD4^+$ levels than do adults (138). Keeping these confounding variables in mind, immunologic classification appears to be useful when based on age-specific $CD4^+$ counts. The current immunologic classification is based on either absolute $CD4^+$ cell counts or the percentage of $CD4^+$ lymphocytes (Table 2) (42). It is suggested by the CDC that if the $CD4^+$ cell count and $CD4^+$ cell percentage place the child in different categories, the more severe category should be used (42).

Clinical Categories for HIV-Infected Children

A child who has been diagnosed with HIV infection can be assigned to one of four mutually exclusive clinical categories. These categories were developed on the basis of signs, symptoms, or diagnoses related to HIV infection (Table 3) (42). Category N patients are not yet symptomatic. Category A and B patients are mildly and moderately symptomatic, respectively, by virtue of any number of criteria set forth in Table 3. The conditions listed for category B (moderately symptomatic) are not exhaustive but include many of the more common examples. Category C patients have one of the AIDS-defining illnesses (Table 4) (42), most of which are discussed in other sections of the review.

NATURAL HISTORY OF THE DISEASE AND PROGNOSTIC FACTORS

Our knowledge of the spectrum of pediatric HIV disease has greatly expanded over the last decade. It is now known that many confounding variables influence the natural history and prognostic factors of the disease. The most important variables include advances in supportive therapies and improvement of antiretroviral strategies. Interpreting prognostic factors related to disease progression in the face of these advancements is difficult, but experience has nevertheless led to a general understanding of the natural history of pediatric HIV.

Important features of HIV disease in children include a variable time of onset and an extraordinarily wide spectrum of clinical manifestations. Young infants may present with signs and symptoms of HIV infection that strongly suggest intrauterine infection, whereas other children may not show outward signs of immunosuppression for many years. Several analyses

TABLE 4. Conditions included in clinical category C for children infected with HIV[a]

Multiple or recurrent serious bacterial infections (septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ)
Candidiasis, esophogeal or pulmonary
Coccidiomycosis, disseminated
Cryptococcosis, extrapulmonary
Cryptosporidiosis or Isosporiasis with diarrhea persisting for >1 month
Cytomegalovirus disease with onset of symptoms prior to 1 month of age
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy in the absence of a concurrent illness other than HIV infection that could explain the findings
HSV infection causing a mucocutaneous ulcer persisting for >1 month; or as the etiology of bronchitis, pneumonitis or esophagitis
Histoplasmosis, disseminated
Kaposi's sarcoma
Primary CNS lymphoma
Lymphoma, Burkitt's, large cell, or immunoblastic
M. tuberculosis, disseminated or extrapulmonary
Mycobacterium infections other than tuberculosis, disseminated
PCP
Progressive multifocal leukoencephalopathy
Toxoplasmosis of the brain with onset at >1 month of age
Wasting syndrome in the absence of a concurrent illness other than HIV infection

[a] Category C is severely symptomatic (Table 3).

of data from pediatric registries (7) and retrospective studies (17, 214) have suggested that the progression of AIDS follows two general patterns in children. In the first year of life, severe immunodeficiency develops in 15 to 20% of infected infants, with serious infections or encephalopathy rapidly intervening. The remaining 80 to 85% have a form of disease that progresses more slowly and is more similar to that seen in adults.

The reasons for rapid disease progression in a subset of infants are not well understood. Early symptoms of HIV disease tend to be predictive of shorter survival (68). *Pneumocystis carinii* pneumonia (PCP), progressive neurologic disease, and early onset of growth failure are all associated with rapid disease progression (140). Some early manifestations, such as lymphocytic interstitial pneumonitis (LIP), hepatosplenomegaly, and parotitis, impart a more favorable prognosis, because they tend to be predictive of slower disease progression (7, 17, 214).

Virologic and immunologic factors that probably affect the prognosis of an HIV-infected child include the timing of infection, the viral load, and the host immune response. Positive viral diagnostics in the first 48 h of life and early development of $CD4^+$ cell lymphocytopenia predict a more rapid rate of disease progression and clinical deterioration. The median survival of pediatric HIV-infected patients ranges from 75 to 90 months, with 70% of children surviving to 6 years of age (68, 238).

Early identification of infants infected with HIV is necessary so that interventions such as antiretroviral therapy and prophylaxis against PCP can be initiated. Identification of HIV infection early in the disease process and regular supportive care are important in improving survival.

CLINICAL MANIFESTATIONS OF PEDIATRIC HIV INFECTION

HIV has the potential to affect all organ systems. Manifestations are diverse and include infectious and noninfectious complications. Pediatric AIDS patients often suffer recurrent serious infections caused by the common bacterial pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus aureus*, and *Salmonella* species. Common viral pathogens are also frequently seen and include herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV). PCP and other opportunistic infections are also encountered. Noninfectious complications seen include dermopathies, progressive neurologic disease, LIP, hematologic dyscrasias such as malignancies, and renal, gastrointestinal, cardiac, and ocular complications. The infectious complications seen in these patients are described in some detail below and are followed by a description of noninfectious complications seen in each organ system.

Infectious Complications in Pediatric AIDS Patients

Infectious complications in pediatric AIDS patients can be divided into two broad categories: common infections of childhood and opportunistic infections. The common infections of childhood are regularly seen in the HIV-infected population.

Bacterial infections in HIV-infected pediatric patients. Bacterial infections are responsible for a substantial degree of morbidity associated with pediatric AIDS. This importance is highlighted by the inclusion of recurrent severe bacterial infections in the 1987 revision of the CDC surveillance definition for AIDS (33). Retrospective reviews of bacterial infections in HIV-infected children provide most of the data in this area. The bacterial infections frequently encountered are similar to those seen in pediatric patients who are immunologically normal (139, 207). Clinical syndromes, by frequency of their occurrence, include bacteremia, urinary tract infection, pneumonia, and skin or soft tissue infections. *S. pneumoniae* is the most common blood isolate from febrile HIV-infected children, accounting for approximately one-third of bacteremias (139). Other isolates in decreasing order of frequency have included *Salmonella* spp., *Enterococcus* spp., *S. aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *H. influenzae*, and others (139).

Infants and children with HIV infection also manifest an increased incidence of acute and chronic otitis media, acute and chronic sinusitis, and recurrent pneumonia. Chronic bacterial otitis media and chronic sinusitis are among the most common infectious complications seen. There have been no systematic studies documenting the microbiology of otitis or sinusitis in these patients. The organisms commonly encountered in other patients with otitis and sinusitis, including *S. pneumoniae*, nontypeable *H. influenzae*, and *Moraxella catarrhalis*, are also usually identified as the causative agents in HIV-infected patients. A growing list of other microbes, both pathogenic and opportunistic, including bacteria, mycobacteria, viruses, fungi, and protozoans, have been identified in this clinical setting as well (53, 249).

Recurrent lobar bacterial pneumonia is also problematic. Causative organisms include *S. pneumoniae*, *Streptococcus pyogenes*, and *H. influenzae* type b. After recurrent bouts of pneumonia, bronchiectasis can be seen, resulting in abnormal pulmonary architecture. This anatomical abnormality further predisposes these patients to lower-airway colonization and recurrent infectious exacerbations. *Mycoplasma pneumoniae* may cause atypical pneumonia but has also been found in children less than 3 years of age with interstitial pneumonia.

The same viruses that cause lower respiratory tract infection in immunocompetent children also infect HIV-infected children; they include respiratory syncytial virus (RSV), parainfluenza viruses, influenza A and B, and adenovirus. RSV is the most common lower respiratory pathogen in childhood and bears some mention in terms of its effect on the HIV-infected population. Published information about RSV infection in this patient population and its clinical presentation includes a case series report (47) and several case reports (27, 64). These reports point out some important features of RSV infection in HIV-infected children. The first is that while the infection may be severe, wheezing may be less common than that seen in immunocompetent children (47). The second feature is that adults with HIV infection can develop interstitial pneumonia secondary to RSV (64). Children and adults with malignancies or who have been pharmacologically immunosuppressed also illustrate the increased pathogenicity of RSV in the presence of defects in B-cell or T-cell function (111, 224).

As might be expected, other respiratory viruses are also common in the HIV-infected child. Parainfluenza virus infection can be severe, and viral excretion can be prolonged (124). Adenovirus sepsis has been found in HIV-infected children with adenovirus pneumonia who subsequently develop fulminant hepatic failure. In addition, adenovirus has been recovered from a surprising number of adult AIDS patients (100).

Mycobacterium tuberculosis (132) infection is of particular concern because of its communicability to health care workers, the emergence of multidrug-resistant organisms, and the potential failure of routine tuberculin skin tests to identify infected patients because of their underlying immunodeficiency. HIV-infected children are at increased risk of tuberculosis not only because of their failing cellular immunity but also because many of them are living with HIV-infected adults who are infected with *M. tuberculosis* (132).

Another unusual cause of pneumonia described in adult AIDS patients is caused by *Rhodococcus equi*, a pathogen that might be expected to emerge in pediatric patients as well (98, 215).

A pediatric AIDS patient presenting with new signs and symptoms of lower airway disease represents a clinical as well as a microbiologic challenge. Sputum samples from very young patients are notoriously difficult to obtain. Frequently, a bronchoscopic evaluation becomes necessary to obtain adequate culture material, particularly if the progression of disease is rapid and/or severe. While empirical antibiotic coverage is often used, open lung biopsy may be needed if the clinical response is not prompt.

Viral infections commonly seen in pediatric AIDS patients. The involvement of common respiratory viruses in pediatric HIV-infected patients has been discussed above. Other viral infections are also seen commonly in this cohort of patients, the most problematic being viruses belonging to the herpesvirus group, particularly HSV, VZV, and CMV.

(i) Herpes simplex virus infections. HSV infection is common in immunologically normal children, with recovery generally being rapid and uneventful (251). Primary infection with HSV-1 may present as gingivostomatitis or may be completely asymptomatic. Following primary infection, the virus becomes latent. Acquisition of HSV-2 usually occurs via sexual contact and is rarely seen prior to the onset of sexual activity.

Reactivation of herpetic disease is markedly enhanced in the face of immunosuppression, so it is no surprise that HIV-infected children can develop severe, chronic, and recurrent HSV disease. Such recurrent disease in AIDS patients results in extensive tissue destruction associated with prolonged virus shedding (236). The most frequent manifestation of recurrent disease is herpes labialis; recurrences tend to increase in frequency as the severity of immunosuppression worsens. As many as 10% of children with AIDS who suffer an episode of primary herpesvirus gingivostomatitis will develop frequent HSV recurrences associated with severe herpetic ulcers (131, 214). HSV can also spread from the oropharyngeal mucosa into the esophagus. The incidence of herpesvirus esophagitis in HIV-infected children is not known, but herpetic lesions in the oropharynx need not be present concurrently (231). Herpetic esophagitis should remain prominent in the differential diagnosis in the clinical setting of retrosternal pain and odynophagia. Such a clinical picture is easily confused with other types of esophagitis, particularly that caused by *Candida* spp. or CMV. Specific diagnosis is made with cultures taken during esophagoscopy.

HSV is notorious for causing central nervous system (CNS) disease, especially in normal newborns. Surprisingly, herpesvirus encephalitis is an infrequent complication in AIDS patients, but when it does occur, it is fulminant and life threatening. Both HSV-1 and HSV-2 have been identified as causative agents (73, 74, 102). The clinical diagnosis of herpesvirus encephalitis is suspected in patients with hemorrhagic encephalitis, especially when it involves the temporal lobes. Brain biopsy may be required to differentiate herpesvirus encephalitis from other infectious and noninfectious entities, including HIV encephalopathy, cryptococcal meningoencephalitis, CNS toxoplasmosis, and primary CNS lymphoma.

Cutaneous and visceral dissemination of HSV infection also occurs, albeit rarely (131, 236). During cutaneous dissemination, large hemorrhagic vesicles and bullae may develop. Prompt treatment of AIDS patients with antiviral therapy when they contract HSV infections decreases the morbidity and the risk of serious complications (131, 231). For children with mucocutaneous recurrences, oral therapy with acyclovir may be considered, and depending on the frequency of the recurrences, the duration of acyclovir treatment may extend from a week of therapy at a time to chronic suppressive daily therapy. These suggestions are based on regimens used in studies of adults with recurrent genital herpes (77). Intravenous therapy is appropriate for all moderate and severe cases, given the potential for dissemination and the poor bioavailability of oral acyclovir. If lesions progress during acyclovir therapy, viral cultures should be repeated and acyclovir susceptibility should be determined. Patients who develop acyclovir-resistant strains may benefit from treatment with vidarabine or foscarnet (89).

(ii) Varicella-zoster virus infections. VZV infection, which is usually self-limited in immunocompetent children, can be very problematic for HIV-infected children. In children with AIDS, the interval between chicken pox (primary VZV infection) and shingles (reactivated VZV disease) may be reduced to weeks or months instead of decades (126, 180). The appearance of shingles in children and young adults serves as a clinical marker for HIV infection in high-risk groups (59) and may be an indicator of progressive cellular immunodeficiency in HIV-infected individuals.

Primary varicella infection in immunocompromised children is known to have a high frequency of visceral complications, with mortality as high as 20% if not treated with antiviral drugs (253). HIV-infected children with low $CD4^+$ cell counts will typically exhibit extensive mucocutaneous disease with persistent new-vesicle formation (126). The course of the disease in these patients can be chronic, progressive, and recurrent.

In the face of primary or reactivated VZV infection, the risk of dissemination warrants antiviral therapy. Acyclovir is considered the drug of choice (2). The optimal dosage and route

of administration vary according to the clinical situation. Clearly, intravenous acyclovir is warranted for severe or progressive disease, because the enteral bioavailability of acyclovir is poor.

Susceptible HIV-infected children who become exposed to VZV should be given immunoprophylaxis with varicella-zoster Ig (VZIG), preferably within 96 h of the exposure. This treatment may not prevent infection, but it can help attenuate the severity of disease (261). Patients receiving intravenous Ig (IVIG) should be protected and need not receive VZIG if the most recent dose of IVIG was administered in the previous 3 weeks (2). Although the currently licensed varicella vaccine is not approved for use in immunocompromised hosts, including those with HIV infection, it is prudent to vaccinate healthy VZV-susceptible contacts to minimize household exposure to varicella. Some experts recommend limiting the exposure of HIV-infected patients to recently immunized children to reduce the risk of secondary cases of vaccine-induced varicella in the immunosuppressed group.

(iii) Cytomegalovirus infections. CMV can be isolated from nearly 60% of children with AIDS. These children are commonly asymptomatic, but some have signs of disseminated CMV disease (213). CMV disease may manifest as interstitial pneumonia, encephalitis, myelitis (107), hepatitis, gastritis, colitis, and/or chorioretinitis (21, 90, 208). Because CMV shedding and asymptomatic CMV infection are so common, distinguishing infection from disease can be a perplexing task. It is often quite difficult to determine if the clinical presentation of an AIDS patient is caused by CMV. Diagnosis of disseminated CMV disease is based on a combination of factors including viral isolation and/or viral antigen detection from the appropriate body fluid in the appropriate clinical setting. Other possible etiologies of the patient's clinical syndrome must be thoroughly investigated concurrently. If CMV is determined to be the culprit, antiviral treatment for CMV can be initiated, although pediatric experience with antiviral drugs having anti-CMV activity is limited (90, 101, 149, 154, 239). Two drugs with in vitro and in vivo anti-CMV activity are ganciclovir and foscarnet. Although these drugs are initially effective for the treatment of CMV retinitis in adults, the benefits are suboptimal (60). There may be some benefit in using the two drugs together when either agent alone is ineffective (24). The effectiveness of hyperimmune CMV-IgG administration with or without ganciclovir or foscarnet is yet to be proven.

Young HIV-infected children with high p24 antigen concentrations have a greater incidence of developing symptomatic CMV disease (48). Two possibilities for this observation are that symptomatic CMV disease is secondary to progressive immunodeficiency or that CMV coinfection may cause more rapidly progressive HIV disease.

Opportunistic infections in pediatric AIDS patients. (i) *P. carinii* pneumonia. The classic opportunistic disease of HIV infection is PCP. This disorder is a diffuse desquamative alveolopathy that results primarily in compromised oxygenation. Most PCP in children perinatally infected with HIV occurs in infants between the ages of 3 and 6 months (147, 222). A strong emphasis has been placed on chemoprophylaxis, because PCP is the most common opportunistic infection in HIV-infected children and the initial episode is frequently fatal (118). The recommendations for PCP chemoprophylaxis and the rationale for some recent changes will be discussed later.

The clinical manifestations of PCP are dependent on age and immune status. Fever may be intermittent. Cough, dyspnea, and tachypnea are seen. The first sign noted by parents of affected infants may be an inability to feed. Hypoxemia progresses to death in nearly all untreated patients. The roentgenographic finding most characteristic of PCP is a reticulogranular interstitial process that progresses to diffuse bilateral alveolar disease. A definitive diagnosis in the appropriate clinical setting relies on the detection of the organism by specialized staining of an endotracheal aspirate, bronchoalveolar lavage fluid, or tissue obtained by open lung biopsy (181).

(ii) *Mycobacterium avium* complex infections. *M. avium* complex (MAC) causes the most common life-threatening bacterial infection in adults with HIV infection (161). Its importance as a cause of progressive wasting associated with HIV in children has recently become clear as well. Two retrospective reviews of MAC infection in large pediatric HIV cohorts have identified $CD4^+$ cell counts of less than 100 cells per μl as the primary risk factor (116, 152). In these studies, as many as 14% of HIV-infected children had MAC infection. Symptoms of MAC infection include fever, night sweats, weight loss, abdominal pain, and anemia, often requiring repeated transfusions. The extent to which these nonspecific findings are directly attributable to MAC infection is difficult to ascertain. Once a patient with AIDS develops disseminated MAC infection, persistent bacteremia with multiple-organ involvement is the rule (256). Therapy is aimed at decreasing symptoms without introducing unacceptable drug toxicities. There remains considerable debate over the optimal treatment regimen for documented disseminated MAC infection, and optimal therapy for children is under investigation. Most experts currently recommend treatment with at least two antimycobacterial drugs, one of which should be a macrolide (clarithromycin or azithromycin) (161). As children with HIV-associated severe immunosuppression live longer, MAC is becoming a major threat to their survival. It should be noted that infection with other atypical mycobacteria, although less common than MAC infection, can cause the identical clinical picture.

(iii) Other opportunistic infections. ***(a) Opportunistic fungal infections.*** As a group, fungal infections make up a significant portion of opportunistic infections. In a review of 30,632 adult and pediatric AIDS patients, 15.4% of the children were found to suffer from esophageal candidiasis (217). Oral candidiasis, usually caused by *Candida albicans*, occurs in 15 to 40% of HIV-infected children. Esophageal candidiasis may coexist with or occur independently of oropharyngeal candidiasis (217). Disseminated candidiasis is uncommon in AIDS patients but does occur. Patients who have central venous catheters and patients who are neutropenic may represent groups at particularly high risk (146).

Meningoencephalitis caused by *Cryptococcus neoformans* occurs in 6 to 13% of HIV-infected adults but is much less common in children with HIV infection (145), affecting only 0.6% of these children (217). Extrapulmonary cryptococcosis can be an AIDS indicator disease, with a clinical spectrum that includes rapidly fatal fungemia, chronic meningitis, and fever of unknown origin.

Certainly, in patients with profound immunodeficiency, a myriad of possible opportunistic fungal infections are possible. The list of case reports involving other fungal infections is extensive and includes mycoses caused by *Histoplasma capsulatum*, *Coccidioides immitis*, *Aspergillus fumigatus*, *Malassezia furfur*, *Sporothrix schenckii*, and others. As our experience with this population grows, it is certain that additional pathogens will join this already staggering list.

(b) Opportunistic parasitic diseases. Although *Toxoplasma gondii* has received considerable attention as a common opportunistic infection of adult AIDS patients, there is a paucity of published information in the pediatric age group because of the apparent rarity of its occurrence. Clinical disease in adults

and older children most commonly presents as encephalitis, presumably because of reactivation of tissue cysts in the CNS.

Gastrointestinal parasites that have been associated with diarrhea and cholangitis in HIV-infected patients include *Cryptosporidium parvum*, *Isospora belli*, *Giardia lamblia*, microsporidia, and others (51, 78, 225). Individually, these opportunistic parasites are uncommon in HIV-infected children, but it is important to remember that they are a potential troublesome group. Some centers in the United States report that as many as 10 to 20% of adult AIDS patients suffer from cryptosporidial enteritis (137), while *I. belli* infestation appears more commonly in the tropical and subtropical climates (66).

While the present discussion of infections seen in pediatric AIDS patients is far from exhaustive, it is representative of the problems encountered. Noninfectious complications of HIV infection are also very common in this cohort of patients. A review of organ systems that are involved in these noninfectious complications follows, with particular attention to the most common entities. Additional infections as they relate to the organ systems discussed will also be introduced.

Organ-Specific Manifestations of Pediatric HIV Infection

Dermatologic manifestations. Common childhood skin infections such as skin and nail candidiasis, varicella, and molluscum contagiosum are seen frequently in HIV-infected children (233). Varicella and its potentially severe complications have already been discussed in some detail. Less serious although bothersome are severe seborrheic dermatitis and other dermatoses (189). As HIV disease progresses, atrophy of skin, nails, and hair may be observed and may reflect chronic malnutrition or the effects of persistent chronic infections.

Drug hypersensitivity reactions occur more frequently in HIV-infected patients than in non-HIV-infected patients (11). Trimethoprim-sulfamethoxazole (TMP-SMX) is the most common offender, although adverse effects may be seen with virtually any drug taken by these patients. Most drug rashes are generalized, pruritic maculopapular eruptions. More severe reactions, including Stevens-Johnson syndrome, can also occur.

Bacillary angiomatosis, a cutaneous papulonodular infection caused by *Bartonella henselae*, was originally recognized in adult AIDS patients (57). Although it has not yet been noted to occur in the context of pediatric HIV infection, it should probably be anticipated. In addition to fever, these patients have hepatosplenomegaly and lymphadenopathy, a nonspecific triad very common to pediatric AIDS patients.

Central nervous system manifestations. Compelling evidence that CNS dysfunction occurs in a large percentage of HIV-infected infants and children has been provided by a number of studies (12, 13, 85–87, 242, 243). A 30 to 40% incidence rate in a cohort of symptomatic children has been estimated by the National Cancer Institute (25). In other series that included asymptomatic, mildly symptomatic, and advanced HIV disease, a 19.6% prevalence rate has been reported (17, 155). A variety of clinical patterns of neurodevelopmental involvement may be seen in HIV-infected children. Progressive encephalopathy, characterized by impaired brain growth, progressive motor dysfunction, and loss of developmental milestones, is commonly encountered. These children display a characteristic motor dysfunction with weakness, flaccidity, hyperreflexia, spasticity, and toe-walking with a wide-based, shuffling gate (12, 13, 87, 242, 243). Cortical atrophy and basal ganglion calcification are often apparent on brain imaging (87). In the majority of cases, no specific infectious etiology is determined other than HIV infection itself. Often, children will progress normally, both physically and cognitively, for a limited period and then plateau developmentally with failure to reach new milestones (12).

The opportunistic CNS infections common to adult AIDS patients, including cryptococcal meningitis and toxoplasma encephalitis, are uncommon in children but do occur (259).

Pulmonary manifestations. The major pulmonary manifestations of HIV infection are infectious and have been discussed above; however, one major clinical entity that appears regularly and is not proven to be infectious is LIP. LIP is a common pulmonary disease that is seen almost uniquely in infants and children infected with HIV (52). It is characterized by diffuse infiltration of the alveoli and small airways by lymphocytes and plasma cells (226, 252). The characteristic noduloreticular pattern seen on the chest radiograph can be confused with infectious forms of pneumonia caused by *Candida* spp., CMV, and *Mycobacterium* spp. The etiology of LIP is unclear, although there is speculation that it may represent an exaggerated local immune response to HIV-infected cells or a response to infection with Epstein-Barr virus. LIP has been considered a favorable prognostic factor of HIV disease, since HIV progresses less quickly when LIP is present. Development of clinical diagnostic criteria has been attempted, but when the diagnosis of LIP is uncertain, as is often the case, biopsy is prudent. Many of the patients who become symptomatic with this complication have a course marked by slowly progressive chronic pulmonary disease, bronchiectasis, and intercurrent pulmonary infections that result in episodes of pulmonary decompensation. Some patients progress to hypoxic respiratory failure (4). The administration of steroids to children with LIP has been associated with the amelioration of symptoms, although no controlled studies have been performed to assess the effectiveness of this therapy (136, 205).

Hematologic manifestations. Hematologic manifestations of pediatric HIV infection include anemia, granulocytopenia, and thrombocytopenia (209). Anemia is the most common hematologic abnormality seen in HIV-infected children, with a reported incidence ranging from 16 to 94% (25, 83, 162, 187, 213, 238). The severity of anemia in these reports has been correlated with the severity of HIV disease, age, and the use of antiretrovirus therapy.

Leukopenia has been observed in 26 to 38% of pediatric patients with AIDS (25, 183, 186). While leukopenia may be seen alone, it commonly occurs in combination with anemia and thrombocytopenia (202). $CD4^+$ cell lymphocytopenia is usually a manifestation of progressive immune deficiency and is generally seen late in the course of disease.

The pathophysiology of the thrombocytopenia that occurs in children infected with HIV is not completely understood. Increased destruction of platelets by immune system-mediated mechanisms, similar to that observed in classic immune thrombocytopenic purpura, may be one explanation. Although there is no correlation between the degree of thrombocytopenia and the progression to AIDS, the incidence of thrombocytopenia is higher in patients with more advanced HIV infection.

Not only do these hematologic dyscrasias complicate the clinical course of HIV infection, but also they often hinder the use of myelosuppressive or myelotoxic drugs that could otherwise play an important role in treating HIV or HIV-related complications. It is often exceedingly difficult to determine which effects are directly related to HIV and which are complications arising from drug-associated toxicities.

HIV-associated malignancies. HIV-associated malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma are far less common in children than in adults. The most common types of neoplasms seen in HIV-infected children are B-cell

lymphomas, particularly of the brain, B-cell lymphoblastic leukemia, and leiomyosarcoma (169). Kaposi's sarcoma occurs only very rarely in children, with 21 reported cases as the AIDS-defining illness among children with AIDS registered by the CDC (39). A recent increase in the incidence of childhood Kaposi's sarcoma in African children infected with HIV is worrisome (262). Several possible mechanisms by which HIV infection predisposes patients to neoplastic diseases are being investigated. Presumably, loss of immune surveillance is crucial, and the constant stimulation by viruses or other infectious agents may act as a cofactor.

Renal manifestations. The occurrence of renal disease in children with asymptomatic and symptomatic HIV infection has been described. Glomerulopathy occurs in up to 15% of children with HIV infection (120, 234), whereas the occurrence of tubular dysfunction is less well defined. Frequent monitoring of these patients, with particular attention during courses of therapy with drugs considered to be nephrotoxic, is necessary.

Gastrointestinal and nutritional manifestations. Failure to thrive is a universal feature of HIV infection in pediatrics. Regardless of the route of infection or length of time the patient is asymptomatic, every child who survives with HIV will eventually fail to grow or will develop weight loss as a major problem. The incidence of failure to thrive ranges from 20 to 80% of symptomatic HIV-infected children (6, 167, 204, 206, 213, 219), and weight loss or growth failure is included in the CDC and World Health Organization clinical case definition of AIDS (42). Chronic fatigue and low-grade fever often accompany the wasting process (212).

In the initial reports of HIV disease in Uganda, a malady termed "slim disease" was distinguished from AIDS and AIDS-related complex by severe wasting and diarrhea (218). Since that report in 1985, it has become clear that gastrointestinal dysfunction and its effect on nutrition, immune status, and growth plays a significant role in the clinical outcome of the HIV-infected individual. This effect is compounded in children because of the importance of nutrition in physical growth and in maturation of the CNS. Because there are many reasons why HIV-infected children might fail to gain weight, it is uncommon to identify one single cause which, when corrected, results in the restoration of normal growth. Decreased intake of nutrients can be caused by many factors including esophagitis, difficulty chewing or swallowing, altered taste from zinc deficiency, depression, or pain. Loss of nutrients also contributes to the malnutrition (260). Vomiting may be caused by gastritis, but the etiology may not be easy to determine. In older children and adults, *Helicobacter pylori* is a prime suspect, but in younger children there may be a lymphoid infiltrate without evidence of a pathogen (19, 159, 245). Chronic diarrhea is probably the most common reason why these patients lose nutrients (260).

Metabolic requirements are increased in HIV-infected individuals because of the frequent fevers, infections, and possibly alterations in metabolic regulation. Cytokines such as tumor necrosis factor and interleukin-1 may play a role in the dysregulation of metabolism in these patients (168). Pharmacologic agents that stimulate appetite have been tried with limited success in HIV-infected adults and to a lesser extent in children. Megestrol acetate (Megace), a tetrahydrocannabinol derivative (Dronabinol), and human growth hormone have each been used to increase weight gain and lean body mass (247). The effectiveness of such agents in the pediatric population has yet to be determined. Nutritional supplementation with a variety of complete or elemental oral supplements can be used. For children in whom enteral nutrition will not meet caloric needs, parenteral nutrition becomes necessary. Intractable pancreatitis or enteritis may improve following a period of parenteral feeding.

Although the specific etiology of failure to thrive, even during periods free of opportunistic infection, is unknown and is probably the result of multiple converging effects, several possible therapeutic interventions have been proposed. A combined effort to optimize nutrition and gastrointestinal absorption, reduce HIV and other infectious burdens, and optimize psychosocial factors may lead to improved growth and weight gain.

Gastrointestinal manifestations of HIV disease may involve any or all of the gastrointestinal tract from the mouth to the colon. Oral manifestations of HIV infection are common. Oral candidiasis is the most common oral lesion seen in HIV-infected children. Three different clinical presentations of oral candidiasis have been described: psuedomembranous candidiasis, erythematous candidiasis, and angular cheilitis (130).

Periodontal disease is also common in HIV-infected children. HIV-associated periodontitis, acute necrotizing ulcerative gingivitis, and necrotizing stomatitis exist as a continuum, each representing progressive stages of worsening periodontal disease (255). The oral pathogens that may be involved in this process include *Porphyromonas gingivalis*, *Prevotella itra-media*, *Fusobacterium nucleatum*, and *Actinobacillus actinomycetemcomitans*. Treatment includes improving oral hygiene and using chlorhexidine gluconate (Peridex) rinses. Antibiotics with activity against oral anaerobes (e.g., clindamycin and metronidazole) may also be necessary.

Recurrent aphthous ulceration occurs in 2 to 6% of the adult HIV-infected population and may be more prevalent in the pediatric cohort (157). These ulcers may be described as minor, major, or herpetiform on the basis of size, duration, and number. They are often very painful. Their presence interferes with chewing and swallowing and can be problematic in children with already impaired nutrition. The antiretroviral drug ddC (dideoxycytidine) has been associated with aphthous ulceration (186). Although not demonstrated by a clinical trial, one suggested regimen for severe painful aphthous ulcers is the administration of a topical glucocorticoid solution. Administration of the steroid should be tapered to decrease the likelihood of sudden recurrence of the ulcers. It is imperative to rule out fungal and viral causes of these lesions prior to the administration of topical corticosteroids.

Esophagitis caused by *Candida* spp., HSV, and other opportunistic pathogens is well recognized in these children. A host of infectious agents may be associated with enteritis or enterocolitis clinically manifest as acute, chronic, or recurrent diarrhea. Any pathogen that infects healthy children may cause difficulty for HIV-infected children. *Salmonella* spp. (29, 150, 228), *Shigella* spp. (10, 18), *Campylobacter jejuni* (81, 184), *G. lamblia*, and rotavirus may cause particularly severe or prolonged disease in HIV-infected patients. Opportunistic organisms including *Cryptosporidium parvum*, microsporidia, *I. belli*, and CMV all occasionally cause severe gastrointestinal disease in AIDS patients (51, 78, 164, 225). Nonspecific HIV enteropathy is also seen on a regular basis and may be due to overgrowth of the normal gut flora secondary to local immunodeficiency and/or frequent antibiotic use. *Clostridium difficile* enteritis can also be encountered, especially given the frequency and duration of antibiotic courses administered to these patients.

Hepatitis may be a manifestation of primary HIV infection, but it is important to investigate the myriad of other possibilities. Some of the common causes of hepatitis in pediatric AIDS patients include infectious etiologies (viral, bacterial,

and opportunistic) as well as drug-induced etiologies. Serologic testing for hepatitis A, B, and C is prudent but may not lead to a diagnosis. Biopsy with appropriate cultures and histologic evaluation should be pursued for progressive or severe cases. Cholestasis, cholecystitis, and pancreatitis can become problematic. Pancreatitis may be secondary to biliary lithiasis, especially in patients who require hyperalimentation, but can also be due to opportunistic pathogens and drug toxicity, particularly from the drugs 2′,3′-dideoxyinosine (ddI) and pentamidine (127).

Cardiac manifestations. Dilated cardiomyopathy is the most frequent major cardiac manifestation in HIV-infected children (153). Severe cardiomyopathy is not common, but when computer-assisted analysis of echocardiography is done, myocardial dysfunction is seen with regularity (153). The primary insult on the myocardium has been ascribed to a variety of causes including HIV infection, opportunistic infection, immune dysregulation, and antiretroviral drugs (125, 156). A myocardial biopsy may be necessary to obtain a definitive etiologic diagnosis so that appropriate therapy can be initiated. If primary HIV is the culprit, additional or alternative antiretroviral therapy may be indicated. Conversely, if the cardiomyopathy is a result of drug toxicity, the drug may need to be withdrawn or changed.

Ocular manifestations. Simple eye infections including blepharitis and conjunctivitis are seen regularly. They should be treated early and aggressively to prevent local spread with orbital involvement.

The severe infectious retinopathies seen in adult AIDS patients are much less common in children (69). The overall incidence of CMV retinitis in pediatric AIDS patients, for example, is 1.2%, while in adults it is 20% (122). The incidence in children increases when their $CD4^+$ cell count drops below 100 cells per μl (122). Children with retinitis often present with bilateral eye involvement late in the course of disease. The late presentation may be ascribed to the rare occurrence of this condition and symptoms that are nonspecific, such as slight diminution of peripheral vision and/or occasional complaints of floaters until central vision becomes affected.

A number of drugs used to treat patients with AIDS and the associated opportunistic infections have been associated with optic neuritis or retinopathy. Some of the drugs included on this list are clofazamine, ethambutol, and ddI. This underscores the importance of monitoring these patients for a myriad of drug toxicities.

Clearly, from the overview provided, the manifestations of HIV infection are numerous and varied. Regular monitoring of the organ systems commonly involved, with help from virtually every pediatric subspecialty, is important in the medical management of these patients.

MEDICAL MANAGEMENT OF HIV-INFECTED CHILDREN

Considerable progress has been made in the development of treatment strategies that have improved the quality and duration of life of infants and children with symptomatic infection due to HIV. To optimize these advances, antiretroviral therapy must be coupled with comprehensive, multidisciplinary care and psychological support. The medical treatment of HIV-infected children is complex and includes the use of antiretroviral drugs, diligent surveillance for the early identification of infectious complications, aggressive appropriate empirical treatment for infectious syndromes followed by specific therapy once microbial identification and susceptibility testing are available, and opportunistic organism prophylaxis, especially for PCP.

Primary Antiretroviral Therapy

To make decisions regarding antiretroviral treatment, it is important to identify infants at risk, to make the diagnosis of HIV infection early, and to assess how quickly the disease is progressing. Since no data yet exist on the subject of using antiretroviral agents in asymptomatic infants, these agents are at present used in patients who have evidence of significant immunosuppression, including but not limited to a low $CD4^+$ cell count for age. Defining the criteria for the initiation of antiretroviral therapy in these patients is complicated by the broad array of clinical and immunological abnormalities that these patients demonstrate. Data from adults and children confirm that the risk of developing opportunistic infections is closely associated with the $CD4^+$ cell count (95, 128). Treatments that either stabilize or increase the $CD4^+$ cell count are likely to delay the onset of AIDS-associated events and prolong survival. Because of age-related differences in $CD4^+$ cell counts for infants and children compared with adults, a set of guidelines different from those used for adults is required. The recommended starting points for the initiation of antiretroviral therapy have been set at age-specific levels that are higher than those previously set for PCP prophylaxis (257). A single determination of $CD4^+$ cell counts should not be used as the basis for a therapeutic decision because of the variations that can be seen when evaluating this parameter. The $CD4^+$ cell counts should be confirmed, allowing the clinician to establish a baseline value. It should be recognized that antiretroviral therapy is recommended for HIV-infected infants and children who develop any AIDS-defining disease manifestation, independent of their $CD4^+$ cell count. The clinical conditions that clearly warrant the initiation of therapy include an AIDS-defining opportunistic infection, failure to thrive, progressive encephalopathy due to HIV, an HIV-associated malignancy, recurrent sepsis or meningitis, thrombocytopenia, and hypogammaglobulinemia (42). There are also a number of other clinical conditions that, depending on the overall status of the patient, may indicate the need for initiating antiretroviral therapy. These conditions include LIP, parotitis, splenomegaly, persistent oral candidiasis despite therapy, unexplained or recurrent diarrhea, symptomatic HIV-associated cardiomyopathy, HIV-associated nephrotic syndrome, HIV-associated transaminitis, chronic bacterial infections, recurrent or persistent HSV or herpes zoster infection, and neutropenia (42).

Zidovudine. ZDV is the most extensively studied antiretroviral agent administered to HIV-infected adults and children. Although it was licensed for use in adults with AIDS in March 1987, it was not approved for use in children with symptomatic HIV infection until May 1990. After trials of efficacy in adults had been completed, clinical trials of ZDV (then AZT) began in the fall of 1986. These initial studies were small (163, 187), but provided the pharmacokinetic, safety, and tolerance data that resulted in approval by the Food and Drug Administration (FDA). The administration of ZDV has clear but variable benefits for infants and children. The measurable clinical effects of ZDV include increased activity levels, weight gain, linear growth velocity, and, perhaps most notably, improvement in neurocognitive function (163). Although ZDV has historically been the mainstay of antiretroviral therapy, it has now become clear that ddI is superior as a first-line antiretroviral agent. The FDA Antiviral Drugs Committee approved ddI as first-line treatment for HIV infection in March 1996 on the basis of results of clinical trials that found ddI to be supe-

rior to ZDV (see below). Approval of combination therapy (ddI and ZDV) was deferred because of the lack of available clinical data.

The recommended dose of ZDV for children aged 4 weeks to 13 years (180 mg/m^2 every 6 h) is higher than that used in adults and is based on the increased frequency of CNS symptoms in children. In pediatric patients also suffering from HIV encephalopathy, the current recommended dose may be suboptimal. Indeed, children suffering from HIV neuroencephalopathy who receive ZDV by continuous intravenous infusion with the goal of maintaining steady-state drug concentrations in the plasma and cerebrospinal fluid show a considerable degree of improvement in neurologic function (65).

The optimal time to initiate antiretroviral therapy in HIV-infected children is not known. Perhaps early institution of therapy, before the onset of symptoms in very young infants, could prevent the neurodevelopmental deficits that occur as the virus replicates in the developing CNS.

In general, ZDV is well tolerated by infants and children, but therapy should be monitored for safety and toxicity. Toxicities of ZDV are predominantly hematologic and include anemia, thrombocytopenia, and neutropenia secondary to drug-related myelosuppression (163, 187). Recombinant erythropoietin and granulocyte colony-stimulating factor have been used to curtail some of these effects, but sometimes a lower dose or alternate antiretroviral agent needs to be considered. Other side effects that occur less frequently include nausea, headache, elevations in hepatic transaminase levels, and myositis. Careful monitoring of children receiving antiretroviral therapy will allow the clinician to identify those children who have evidence of toxicity and those who have progression of disease. In either case, a change in antiretroviral therapy may be warranted.

A decreasing susceptibility of HIV to ZDV has been described in pediatric patients. Children with isolates resistant to ZDV have worse clinical outcomes than do children whose isolates remain susceptible over time (174). This was determined by a 50% decline in CD4$^+$ cell counts after 1 year of treatment, failure to thrive, or death. Children with resistant viruses who are given alternative antiretroviral treatment respond to the new treatment with improved growth and stabilization of their HIV-related disease (174). These data suggest that in HIV-infected children, ZDV-resistant HIV strains are associated with diminished drug efficacy and more rapid disease progression. As the resistance of HIV to ZDV increases, it is possible that more infants will also be born with a ZDV-resistant strain, necessitating consideration of other therapies.

2′,3′-Dideoxyinosine. Studies of ddI in children began at the National Cancer Institute in 1989, just months after the initiation of phase I trial in adults. The simultaneous approval of ddI by the FDA in October 1991 for both children and adults was a milestone in pediatric drug development. A very important preliminary observation from the ACTG 152 trial was that ZDV monotherapy was inferior to ddI alone or in combination with ZDV in terms of time to progression of disease. ddI is the only other antiretroviral agent currently approved for pediatric use, and until recently it was used only as a second-line therapy for children who are intolerant of ZDV or whose disease progresses while they are taking ZDV (25, 56). In light of the results of the ACTG 152 trial, ddI has been approved by the FDA as first-line therapy for HIV infection. As more data regarding the use of combination regimens (e.g., ddI and ZDV) become available, recommendations for initial therapy may change.

Like ZDV, ddI is a nucleoside analog. It has less severe myelotoxicity (25), but pancreatitis has been reported in 13% of pediatric patients being treated with it (26).

Other available antiretroviral drugs. Zalcitabine (ddC) is another nucleoside analog that inhibits reverse transcriptase. It has been approved for use in adults in combination with ZDV. Experience with ddC is limited in children, but through the ACTG, trials are in progress to gather data on the safety and efficacy of ddC when used in concert with ZDV. The negative enantiomer of ddC, Lamivudine (3TC), is also undergoing clinical trials in children.

A number of nonnucleoside reverse transcriptase inhibitors have been developed. These drugs are chemically distinct from the nucleoside analogs but have in common a high degree of antiretroviral activity with minimal toxicity (165, 201, 235). Results of clinical trials with children are not yet available.

Agents that interfere with other critical points of the HIV life cycle are also being evaluated as potential anti-HIV therapies. Studies evaluating recombinant soluble CD4 showed that it was safe and well tolerated in adults and children but failed to show significant antiretroviral activity (119). While no data are yet published on the clinical use in pediatrics of a new class of antiretroviral agents, the protease inhibitors, the data obtained in studies of adults look promising (63, 134, 160). Phase I trials in children that will evaluate the safety of two protease inhibitors, KNI-272 and MK 639, are just beginning.

Future of antiretroviral therapy. Progress in the development of antiretroviral therapy for pediatric HIV patients will probably be in the form of combination regimens that enhance and expand the activity of currently available antiretroviral drugs. It is possible that combination therapy, through impacting on the different components of the HIV life cycle, will help overcome some of the emerging problems with drug resistance.

Supportive and Prophylactic Therapy

***P. carinii* pneumonia prophylaxis.** PCP most often occurs in the first year of life, with a median presentation at 3 to 6 months (147). The initial episode is frequently fatal and underscores the importance of PCP prevention in HIV-infected infants. The 1991 CDC guidelines emphasized the need for prompt identification of infants born to mothers infected with HIV, with serial measurements of their CD4$^+$ cell counts (35). Initiation of PCP prophylaxis was recommended if the infant CD4$^+$ cell count fell below age-adjusted normal counts (34). Presently, many HIV-exposed children are not identified early enough to provide prophylaxis during the period of highest risk for PCP. A study of HIV-infected children diagnosed with PCP in the United States during 1991 to 1993 indicated that 59% of children were not identified early enough for the initiation of prophylaxis (221). Failure to identify pregnant women with HIV infection and to subsequently monitor the infants born to these mothers substantially limits the effectiveness of PCP prophylaxis. Approximately 10% of children diagnosed with PCP in the first year of life have CD4$^+$ cell counts greater than 1,500 cells per μl, the age adjusted threshold previously suggested for the initiation of prophylaxis. This percentage may be even higher, particularly in the infants less than 6 months old (93, 221). Perhaps more critical is the fact that CD4$^+$ cell counts can drop very rapidly during the first few months of life, limiting their usefulness in determining the need for prophylaxis in this age group.

New published recommendations take into consideration many of the issues put forth. The new guidelines suggest that all infants born to HIV-infected mothers should start taking PCP prophylaxis at 4 to 6 weeks of age, regardless of their

$CD4^+$ count. Infants who are first identified as being HIV exposed after 6 weeks of age should be given prophylaxis immediately (44). PCP prophylaxis is not recommended before 6 weeks of age because of the very low risk in this group, as well as the potential toxicity of sulfa drugs in newborns as a result of their immature bilirubin metabolism. In addition, the use of ZDV in the first 6 weeks of life to decrease perinatal transmission of HIV does cause drug-related anemia, an effect that may be more pronounced if sulfa-containing drugs and ZDV are used together.

All HIV-infected infants and infants born to HIV-infected mothers whose status has not yet been determined should continue taking PCP prophylaxis through their first year of life (44). At that time, prophylaxis can be discontinued among infants in whom HIV infection can be reasonably excluded. All HIV-infected children over the age of 1 year should continue to have regular $CD4^+$ cell monitoring to determine if there is a need to continue prophylaxis. Any age-dependent $CD4^+$ cell measurement that indicates severe immunosuppression (Table 2) (42) in the first year of life is grounds for continuation of prophylaxis. Children for whom prophylaxis is discontinued should be routinely evaluated for severe immunosuppression by measurement of their $CD4^+$ cell count. When laboratory evidence of progressive immunosuppression occurs, PCP prophylaxis should be reinstituted (44). Children who have had an episode of PCP require lifelong prophylaxis to prevent recurrence regardless of their $CD4^+$ cell count or clinical status.

Currently, the drug of choice for PCP chemoprophylaxis is TMP-SMX (42). If this drug is not tolerated, an alternative drug such as dapsone or pentamidine can be introduced. Although TMP-SMX has been shown to substantially reduce the risk for PCP among HIV-infected children, clinicians should be aware that some children have developed PCP despite the use of recommended prophylaxis (170). Prophylaxis may fail because of noncompliance, malabsorption of the medication, or true drug failure.

Prophylaxis against other opportunistic infections. Comprehensive guidelines for the prevention of the most prevalent and life-threatening opportunistic infections in persons infected with the HIV virus have recently been developed by the CDC and the Infectious Disease Society of America (244). Specific notes on guidelines for pediatric patients are included in every section, although in the majority of cases, firm pediatric recommendations await the results of controlled clinical trials.

Other opportunistic infections for which prophylaxis is available include MAC infections, recurrent HSV infection, VZV infection, and recurrent mucocutaneous candidiasis.

Rifabutin for MAC prophylaxis in adults has no effect on mortality but is well tolerated, and there is a significant decrease in MAC bacteremia when the drug is administered (172). Recently published guidelines suggest a threshold $CD4^+$ cell count of 75 cells per μl for the initiation of MAC prophylaxis (rifabutin), with some adjustment for children less than 6 years of age (244). There is an ongoing phase I study to investigate the pharmacokinetics of rifabutin in children. Recommendations for its routine use for prophylaxis await the results of clinical trials.

Because acute episodes of HSV infection can be treated successfully, chronic acyclovir therapy is unnecessary after lesions resolve; however, persons with frequent or severe recurrences can be given prophylaxis with daily suppressive acyclovir therapy. Acyclovir prophylaxis may also be helpful for patients with recurrent VZV infections (244).

Chronic mucocutaneous candidiasis can be problematic, especially when it interferes with the ability of the child to eat. Suppressive therapy with a systemic azole, such as fluconazole, should be considered for infants with severe recurrent mucocutaneous candidiasis (244). It should also be considered for patients with recurrent esophageal candidiasis.

Multiple-organism prophylaxis seems prudent, and clinical trials are being done in adults and children to assess their benefit. A phase II study in adults is evaluating the combination of three antimicrobial agents: TMP-SMX; clarithromycin, a macrolide antibiotic with anti-MAC activity; and atovaquone, an antiparasitic agent that has antitoxoplasma and pneumocysticidal activity. A similar pediatric trial, ACTG 254, is comparing the combination of azithromycin and atovaquone to conventional TMP-SMX prophylaxis. Further work in this area needs to be done before multiple organism prophylaxis can be recommended in the pediatric age group.

Prophylaxis against common bacterial infections. The value of pooled human IVIG in pediatric AIDS patients has been evaluated in several clinical trials. Prior to the initiation of routine PCP prophylaxis, pediatric patients with $CD4^+$ cell counts greater than 200 cells per μl demonstrated a substantial decrease in the frequency of serious bacterial infections when treated monthly with IVIG (171). A more recent study examined the effects of IVIG on the prevention of serious bacterial infections in children taking ZDV (227). The results of this trial did not show an advantage for those treated with monthly IVIG if they were also receiving TMP-SMX for PCP prophylaxis, raising the possibility that patients treated with TMP-SMX will not benefit additionally from IVIG administration. Despite these findings, there does appear to be a role for IVIG in a subset of pediatric AIDS patients. The Working Group on Antiretroviral Therapy has recommended the use of IVIG therapy in combination with an antiretroviral agent for children with humoral immunodeficiency (257). Included in this group are children with hypogammaglobulinemia (IgG level in serum of less than 250 mg/dl), children with recurrent serious bacterial infections (e.g., bacteremia, meningitis, and pneumonia), children who fail to form antibody to common antigens, and children living in areas where measles is highly prevalent who have not developed an antibody response to measles vaccine after two doses of measles vaccine. In addition, children with bronchiectasis who continue to suffer from recurrent pulmonary infections despite treatment with a standard regimen of cyclic antibiotics and aggressive pulmonary toilet might benefit from adjunctive IVIG therapy.

Routine vaccinations. Routine childhood vaccines are important for pediatric patients who are infected with HIV. In general, live viral vaccines (oral polio and varicella) and live bacterial vaccines (Bacille Calmette-Guérin) should not be given to patients with AIDS or other clinical manifestations of HIV infection (2). Measles, mumps, and rubella vaccine (MMR), a live attenuated viral vaccine, is an exception. The occurrence of severe measles in asymptomatic and symptomatic HIV-infected children, together with the lack of reported serious or unusual reactions to immunization with MMR vaccine, has led to the recommendation that these patients should receive MMR vaccine. Although MMR is usually administered at 12 to 15 months of age, if the risk of exposure is increased, such as during measles outbreaks, vaccine can be given to younger children (2).

Inactivated polio vaccine offers an alternative to the live attenuated oral polio vaccine; however, the live attenuated varicella vaccine recently approved by the FDA should not be administered to children with immunodeficiency, including patients with AIDS or HIV-associated immunologic abnormalities. Moreover, given that the licensed varicella vaccine is a live attenuated VZV strain, it is prudent for pediatric AIDS pa-

tients to avoid contact with recent vacinees. For routine immunizations in the HIV-infected pediatric patient, diphtheria toxoid, pertussis, and tetanus toxoid, hepatitis B vaccine, *H. influenzae* type b conjugate vaccine, inactivated polio vaccine, and MMR should be given according to the usual immunization schedule (2). Pneumococcal vaccine administered at 2 years of age and influenza vaccine administered yearly starting at 6 months of age are also recommended (2). It should be noted that HIV replication has been demonstrated to increase transiently in patients who are immunized with influenza vaccine (171a), raising concern about the appropriateness of this vaccine in HIV-infected patients.

In general, children with symptomatic HIV infection have poor immunologic responses to vaccines (20). Hence, such children, when exposed to a vaccine-preventable disease such as measles, tetanus, or varicella, should be considered susceptible regardless of their immunization status and should receive appropriate passive immunoprophylaxis if indicated.

CONCLUDING REMARKS

The number of HIV-infected infants and children continues to increase worldwide. Clearly, prevention of HIV infection in this age group starts with preventing HIV infection in adults, because most cases of childhood HIV infection are acquired vertically. While these efforts desperately need to continue, the identification of pregnant women who are HIV infected needs to be aggressively pursued. Attempts to interrupt vertical transmission can be successful, as shown by the ACTG 076 trial, but further advances are needed. Frequent clinical and laboratory follow-up of exposed infants is mandatory to determine whether they are infected, so that antiretroviral treatment and appropriate prophylaxis for infections can be initiated. Therapy for HIV infection can both prolong and improve the quality of life. New classes of antiretroviral agents and new immunomodulating drugs are being developed. Optimal prophylaxis against bacterial and opportunistic infections continues to evolve. Critical to the development of optimal therapies is the enrollment of all eligible patients into appropriate clinical trials. Information and eligibility criteria for ongoing studies are available from the Pediatric Clinical Trials Group, Pediatric Branch, National Cancer Institute, by calling (800)-TRIALS-A.

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