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Preventing and Managing HIV Infection in Infants, Children and Adolescents in the United States

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Abstract

Objectives—After completing this article, readers should be able to:

1. Recognize the important role that the pediatrician plays in the prevention, detection, and care of human immunodeficiency virus (HIV)-infected and -affected patients.
2. Know the epidemiology of human immunodeficiency virus infection in infants, children and adolescents.
3. Select the proper HIV diagnostic testing plan for infants, children and adolescents.
4. Plan the comprehensive management of HIV-exposed infants.
5. Recognize the clinical conditions suggestive of HIV infection, including the major opportunistic infections seen in patients with HIV/AIDS.
6. Understand the principles, monitoring, and complications of HIV treatment in infants, children and adolescents.

Practice Gap—Effective prevention strategies have reduced the risk of perinatal transmission of HIV infection to less than 1–2% in the United States, but failures to fully implement these strategies result in continued, preventable infant HIV infections. In addition, the rising number of sexually acquired HIV infections in adolescents underscores the important role of the pediatrician in preventing and diagnosing HIV infection in youth.

Keywords

HIV; antiretroviral; immunodeficiency; opportunistic infections; prevention; adolescents

Since the first description of infants with HIV infection in the early 1980s [1,2], there have been tremendous advances in the understanding, prevention and treatment of HIV infection. Effective prevention strategies have reduced the risk of perinatal transmission, or maternal-to-child transmission (MTCT), of HIV infection to less than 1–2% in the United States and the WHO has made global elimination of new infant HIV infections a realistic target by 2015 [3]. For those children who have HIV infection, the development of potent antiretroviral (ARV) drugs has transformed a once progressive and often fatal infection for

children into a chronic condition with dramatically reduced morbidity and expectations for long and productive lives.

Epidemiology of Pediatric HIV Infection

Worldwide, an estimated 34 million people are living with HIV infection; 3.4 million, or about 10%, are under 15 years old. [4] Nearly all (95%) children under 15 years old acquired HIV infection perinatally; in fact, a substantial number of the 2 million adolescents (10–19 years old) with HIV infection worldwide are thought to be long-term survivors of perinatal HIV infection, but data have not been collected in a way to distinguish perinatal (vertical) and behavioral (horizontal) routes of HIV transmission in this age group [5].

As of 2011, in the United States, 4500 children (<15 years old) had perinatal HIV infection, but this number represents about half of all perinatally infected HIV-infected people in the US, since diminishing numbers of new infant infections and markedly improved long-term survival of children with perinatal HIV infection have meant that most perinatally infected children are now adolescents and young adults [5–7].

The predominant route of HIV infection in children is MTCT, including intrauterine, intrapartum, and postnatal (through breastfeeding) transmission. In the absence of ARV preventive interventions, in non-breastfeeding populations, 25–30% of infants born to HIV-infected women will become infected; the risk increases to as high as 50% for infants with prolonged breastfeeding. Sexual transmission is an important mode of transmission for adolescents, especially for adolescent girls in settings with generalized HIV epidemics and for young men who have sex with men. Less common routes of transmission include transfusion with blood products tainted with HIV (before routine screening of blood products for HIV was established); percutaneous exposure; and, rarely, HIV-infected caretakers chewing or warming food in their mouths and then feeding it to infants and children [8].

HIV: pathogen and pathogenesis

HIV type 1 (HIV-1) and HIV type 2 (HIV-2) are enveloped, single-strand RNA retroviruses. HIV-1 is overwhelmingly responsible for HIV infections worldwide, including the US. HIV-2 causes infection predominantly in people from parts of West Africa but it is less transmissible and generally associated with lower levels of viral replication and less severe disease [9].

The principal targets of HIV are cells expressing the CD4+ molecule: CD4+ T lymphocytes (CD4 T cells) and monocytes/macrophages. HIV binds the CD4 target together with a cellular coreceptor (CCR5 or CXCR4), resulting in virus envelope fusion with the host cell wall that permits viral entry into the cell. CD4+ cells in the gut are a major target and the virus disseminates widely soon after infection, including to the central nervous system. CD4 T cell infection is followed by viral replication, release of HIV virions, and CD4 T cell death, leading over time to progressive CD4 T cell depletion and impairment of cellular immunity, the hallmark of HIV-related immunodeficiency.

In a small proportion of CD4 T cells, HIV entry instead leads to integration of the HIV genome (HIV RNA reverse-transcribed to a DNA sequence) into the cellular genome of a CD4 T cell that enters a quiescent phase as a memory CD4 T cell, harboring its latent HIV infection for activation months or years later. Such latent infection of long-lived memory T cells underlies a main barrier to sterilizing cure of HIV infection [10].

Preventing HIV infection in infants, children and youth

The most important strategies to prevent MTCT in the United States have been: administering ARV drugs to HIV-infected mothers and their infants; elective Cesarean section for HIV-infected women who reach term without achieving plasma HIV virologic suppression; and providing replacement feeding instead of breastmilk to infants of HIV-infected mothers. In settings outside the United States where infant replacement feeding confers an unacceptably high risk of HIV-unrelated morbidity and mortality (including in many sub-Saharan African countries), the additional strategy of administering ARVs (to mothers or infants during breastfeeding has become an effective means to allow breastfeeding while reducing the risk of HIV transmission. In the US, however, all HIV-infected women are still advised against breastfeeding, regardless of ARV use and maternal plasma HIV suppression, because neither maternal nor infant ARV prophylaxis completely eliminates breastmilk HIV transmission (residual transmission can be as high as 5%) and safe and affordable replacement feeding is available in the US [11, 11a].

The ability of ARV drugs to prevent MTCT was first demonstrated in the landmark ACTG 076 trial demonstrating that zidovudine (ZDV) administered during pregnancy, intrapartum and (to the infant) after birth could cut transmission from 26% to 8% in the absence of breastfeeding [12]. Subsequent studies demonstrated even greater efficacy for combination ARV therapy (cART), comprised generally of at least 3 ARV drugs from at least 2 different classes. Routine use of cART for pregnant women in the US has resulted in MTCT risk less than 1–2% and estimated annual new infant infections numbering no more than 100–200 nationwide [13]. In fact, pregnant women who achieve consistent plasma HIV virologic suppression during pregnancy are at such low risk of MTCT that neither elective Cesarean section nor intrapartum ARV (intravenous zidovudine) is recommended to further reduce transmission risk [11]. However, failure to identify HIV infection in pregnant women, barriers that prevent HIV-infected women from taking cART during pregnancy, and incident HIV infection in pregnant and breastfeeding women remain important problems that contribute to residual infant infections in the US [13,14].

The latest recommendations by the US Department of Health and Human Services for preventing MTCT in the United States can be found at http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines [11]. The comprehensive prevention approach is multipronged: routine testing for HIV in pregnant women; administering ARV drugs to HIV-infected pregnant women and their infants; supporting women's retention in care and adherence to cART; offering elective cesarean section to women who have not achieved HIV plasma viral RNA concentration (viral load) < 1000 copies/mL by the end of pregnancy and minimizing invasive obstetric procedures (eg, fetal scalp electrode); avoidance of breastfeeding; primary

prevention of HIV infection in women of reproductive age; and ensuring access to family planning services for HIV-infected women.

HIV testing is recommended as early as possible in each pregnancy, including for women who tested HIV negative in a prior pregnancy. Retesting in late pregnancy should be considered for all HIV-seronegative women and is recommended for pregnant women who are at high risk of HIV infection, such as women with a known HIV-infected partner, history of injection drug use, STI diagnosis signs/symptoms of acute HIV infection; women who reside in jurisdictions with elevated HIV incidence among women of childbearing age (≥17 HIV cases per 100,000 person-years); and women receiving health care in facilities with at least one diagnosed HIV case per 1,000 pregnant women per year [15, 15a]. Women presenting in labor who have not received appropriate HIV testing in pregnancy should undergo rapid HIV antibody testing. If the results are positive, a confirmatory HIV test should be performed as soon as possible and maternal/infant ARV drugs should be initiated pending the confirmatory test result. If the confirmatory HIV test is positive, infant ARV drugs should be continued; if the test is negative, then infant ARV drugs should be stopped.

Newborn nurseries should have procedures in place to alert nursery staff when an HIV-exposed infant is born, since neonatal ARV prophylaxis should be initiated as soon after birth as possible, ideally within 6–12 hours. [See **Management of HIV-exposed infant**.] Upon admission to the newborn nursery – and at the first newborn outpatient visit - documented maternal HIV testing results should be confirmed. For a newborn whose mother did not receive appropriate HIV testing in pregnancy, HIV exposure status should be confirmed by performing rapid HIV antibody testing on the mother; if maternal testing cannot be performed, infant antibody testing should be performed to assess potential HIV exposure. If rapid maternal or infant antibody testing is positive, the infant should initiate ARV drugs immediately, pending confirmatory testing, as for women with positive rapid antibody testing during labor/delivery (see above).

Recognizing HIV infection in infants, children and adolescents: Routine testing and Clinical presentations

HIV infection should be suspected in patients presenting with typical clinical findings, but many children and youth are diagnosed before clinical manifestations develop because of several routine indications for HIV testing.

Indications for Routine HIV Testing

All infants born to women with HIV infection should undergo a scheduled series of HIV virologic tests that will lead to confirmation or exclusion of perinatal HIV infection (see Management of HIV exposed infant). If the maternal HIV status has not been determined, maternal HIV antibody testing (or, if mother not available, infant HIV antibody testing) should be requested to determine if the infant is HIV exposed.

Many new cases of HIV infection in infants and children in the US are diagnosed in children who were born outside the US, especially in high HIV prevalence settings like sub-Saharan Africa [16]. Some of these children have come to the US with their mothers/families while

others have been adopted. HIV antibody testing should be offered to foreign-born children (particularly from settings of moderate or high HIV prevalence) to evaluate for infection (in those 18 months and older) or for perinatal exposure (in those under age 18 months); those under age 18 months who are HIV antibody positive will require additional HIV virologic testing, as for HIV exposed newborns, to assess if they are HIV infected (see **HIV testing in infants, children and adolescents**).

Clinicians caring for infants and children with HIV exposure or infection should ensure that the siblings of these patients have also been evaluated for HIV infection. For instance, when managing an HIV-exposed infant, the clinician should recommend to the mother that she have her other children tested for HIV infection – even if they appear healthy – unless there is documentation that she did not have HIV infection at the time she was pregnant with or breastfeeding those older children. While unusual, some undiagnosed (and thus untreated) perinatally HIV-infected children have survived into their teens without serious illness, so there is no upper age limit for siblings to be considered for HIV testing.

Adolescents—CDC recommends performing an HIV test routinely beginning at age 13 years, USPSTF guidelines recommend routine screening beginning at age 15 years, and the AAP recommends HIV testing at least once by age 16–18 years in patient populations with HIV prevalence ≥ 0.1% [15, 17, 18]. Thus, routine HIV screening is recommended for nearly all adolescents at least once, even in the absence of specific risk factors. The indications for and intervals between subsequent HIV testing are determined by level of risk. Those at very high risk should be offered HIV testing at least annually, while an interval of 3–5 years is reasonable for those at elevated but lesser degree of risk [15]. Important indicators of very high risk include young men who have sex with men (MSM) and intravenous drug users. Other adolescents at increased risk of HIV infection include those whose sexual partners are MSM, intravenous drug users or HIV-infected; those who report unprotected anal or vaginal sexual intercourse; those who have sexually transmitted infections (STIs); and sexually active youth who live in an area of increased HIV prevalence (defined by the CDC as a community with an HIV seroprevalence of at least 1%).

Clinical presentations that warrant HIV Testing

Many infants and children with HIV infection may have prolonged periods without severe illnesses or clinical manifestations of HIV infection. However, perinatally infected infants (especially those infected in utero) are at high risk of rapid progression to severe illness and death. While full implementation of PMTCT policies should prevent nearly all infant HIV infections and identify early those few infections that occur despite appropriate interventions, there are still infants and children whose perinatal HIV exposure and resulting infection have escaped detection; it is therefore important for clinicians to recognize specific infections and clinical presentations that may be a sign of unrecognized HIV infection (or other immunodeficiency). TABLE 1 summarizes the clinical manifestations of untreated HIV infection.

Pneumocystis pneumonia (PCP), caused by the fungus *Pneumocystis jirovecii* (formerly *carinii)*, was among the most common and deadly presentations of HIV infection in infants

early in the epidemic [19]. Rare in the first month of life, this condition peaks at ages 3–6 months. Infants present with progressive cough, poor feeding, dyspnea and often fever. Onset can be gradual or abrupt but progression to hypoxia, respiratory failure and death will occur without prompt recognition and treatment [20].

Mucosal candidiasis is a common and early sign of HIV infection in untreated infants. While an episode of oral thrush can occur in infants without immunodeficiency, oral candidiasis that is severe, persistent or recurrent is an important manifestation of the cellular immune dysfunction caused by HIV infection and other diseases causing immunodeficiency.

Recurrent bacterial pneumonia and other bacterial infections (sinusitis, otitis) were common in HIV-infected infants and children before cART and may be the first clue to unrecognized HIV infection. While these infections generally have similar presentations and pathogens (especially pneumococcus) in HIV-infected and uninfected children, their increased frequency and recurrence are typical in children with HIV infection.

The constellation of persistent parotid gland swelling, lymphadenopathy and chronic interstitial lung disease (lymphocytic interstitial pneumonitis, LIP) was a typical pattern in pediatric HIV infection, often in those untreated children who were spared more serious infections in the first few years of life.

Growth monitoring and neurodevelopmental screening, essential aspects of standard pediatric primary care, may reveal failure to thrive, stunting or abnormal motor and cognitive development that may be important clues to untreated HIV infection in infants and children.

All children with tuberculosis disease should be tested for HIV infection. Adults with HIV infection are more likely to develop contagious TB disease, increasing the risk of TB infection in children in their households. HIV-infected children who acquire TB infection are then more likely to develop TB disease because of their HIV-related immunologic impairments.

Herpes zoster (shingles) is uncommon in children, but most children who develop it probably do not have an immunodeficiency disorder. Children with untreated HIV infection, however, frequently develop zoster. In the US, where unrecognized HIV infection in children is fortunately rare, an episode of zoster may not warrant automatic HIV testing. However, an episode of zoster in a child does merit thorough review of the child’s history of other illnesses, careful physical examination and ascertainment of health status of mother and siblings in order to determine if HIV testing is warranted. Clinicians should have a low threshold for performing HIV testing in children with zoster that is severe or recurrent

In adolescents, the diagnosis of a new STI should prompt HIV testing. HIV infection does not directly increase the risk of contracting STIs but an incident STI is a marker of the same sexual risk behavior that increases the risk of HIV transmission.

Those who care for adolescents, including pregnant and breastfeeding women, should be able to recognize presentations of primary HIV infection, the period of several days to

weeks following incident HIV infection when HIV viremia (and potential for transmission to others) is high and HIV antibodies have not yet appeared. Most (50–90%) episodes of primary HIV infection are symptomatic, but the variable severity and non-specific “flu-like” or “mononucleosis-like” nature of acute retroviral syndrome often result in patients not seeking medical care for their illness and/or clinicians not recognizing it as possible primary HIV infection [21]. The most common features include fever, vomiting, diarrhea, headache, myalgias, lymphadenopathy, and rash (TABLE 2). Sexually active patients with lymphadenopathy, maculopapular rash and shallow, sharp ulcers of the oral and/or anogenital mucosae should be evaluated for acute HIV infection. Since this early phase of HIV infection precedes the full antibody response, patients with suspected acute HIV infection should be tested with a fourth generation antigen/antibody test or a plasma HIV RNA test (see HIV Testing Assays). Patients diagnosed with acute HIV infection should be counseled about their high risk of transmitting HIV through unprotected sexual contact with others; HIV specialists should be consulted promptly for recommendations regarding HIV treatment. Because of the high risk of MTCT after acute HIV infection in pregnancy or during breastfeeding, pregnant women with acute HIV infection should be urgently referred for comprehensive care and ARV initiation, and breastfeeding women with acute infection should be counseled to stop breastfeeding immediately, be referred for their own care and have their infants undergo evaluation for HIV infection.

PreTest Counseling and Consent for Testing

Patients who meet criteria for routine HIV screening (eg, pregnant women and initial testing for adolescents) should be notified that HIV testing is recommended but given the option to decline testing [15]. HIV testing provides an important opportunity to educated patients about HIV and to counsel them about sexual practices and other behaviors that may elevate their risk of HIV infection. However, mandatory HIV prevention counseling and separate written consent for HIV testing can be barriers to HIV testing and are not recommended [CDC 2006]. Clinicians should be familiar with their local laws and regulations, as some jurisdictions and institutions continue to require such counseling and/or written consent in order to proceed with testing [22]. The clinician should make a clear plan with the patient for delivering the test results, including timing (if not using rapid testing), location (usually best to discuss results in person), who else (eg, parents, partners, friends) should or should not be present for discussion of results, and what additional confirmatory testing will be needed if initial test results are positive.

In most cases, the plan for HIV testing of perinatally exposed newborns has been discussed with the mother (and often other caretakers) even before the infant’s birth. However, each clinical encounter with the infant and family is an opportunity to review the HIV testing plans and the interpretation of available results..

In older children for whom HIV testing is indicated (usually those who escaped detection in infancy), the discussion of the purpose and plan for testing will depend on the age of the child and must take into account how to respect the (HIV-infected) mother’s feelings about discussing her own HIV diagnosis with the child and other family members. This process is

best handled by an interdisciplinary team (eg, physician, nurse, and social worker) experienced with such situations.

HIV testing assays in infants, children and adolescents

Several assays are available for diagnostic HIV testing (TABLE 3); assay selection depends on availability, desired turnaround time, age and suspicion of acute HIV infection.

The current standard HIV diagnostic testing for children (≥ 18 months old), adolescents and adults (including pregnant women) relies upon detection of HIV antibody in a blood specimen in two steps: a screening enzyme-linked immunoassay (EIA) is performed first, and if reactive, a confirmatory HIV antibody test such as Western blot is then performed. Both tests must be positive to meet the criteria for HIV infection. Rapid, point-of-care EIA assays are available for detecting HIV antibodies in blood and saliva specimens; negative results reliably exclude established HIV infection as well as standard EIA tests (none is sensitive for detecting acute HIV infection), but positive tests need to be confirmed with standard HIV diagnostic assays.

Newer "4th generation" HIV testing assays that detect the HIV p24 antigen and both IgM and IgG antibodies to p24 antigen, have higher sensitivity, especially for identification of recent HIV infections [23]. The CDC is anticipated to update their guidelines to recommend use of these 4th generation assays as the preferred initial test to screen for HIV infection (for those at least 18 months of age) and most experts prefer this assay to traditional antibody assays when acute HIV infection is suspected.

Virologic testing includes assays that detect HIV antigens (including the 4th generation antigen/antibody assays discussed above) and those that detect HIV DNA (by polymerase chain reaction, PCR) or HIV RNA (by PCR and other methods). These assays are important diagnostically for (1) recent/primary HIV infection, when viremia is present but antibody is not; and (2) in infants (up to age 18 months), in whom the presence of passively transferred maternal HIV antibodies requires virologic detection to identify those infants who are infected. The DNA PCR detects intracellular proviral DNA, the result of viral reverse transcriptase transcribing HIV RNA to DNA in the host cell. The HIV DNA PCR test is used almost exclusively for infant diagnosis, though the DNA PCR or RNA assays are equally acceptable for this purpose. Antigen/antibody assays should not be used for infant diagnosis. HIV RNA assays and antigen/antibody assays are both appropriate for detecting primary HIV infection. Quantitative HIV RNA assays are also routinely used for monitoring of response to ART in HIV-infected people and may be more widely available than the DNA PCR assays.

Management of HIV-exposed infants

Primary medical care providers for infants should know how to manage the HIV-exposed infant. The components of special care for such infants include: ARV prophylaxis; HIV diagnostic testing; evaluation for need for PCP prophylaxis; routine immunizations; monitoring for manifestations of HIV infection; and reinforcing education and counseling

for mother/family. Detailed, regularly updated guidelines for managing HIV-exposed infants are available at http://www.aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0.

Neonatal ARV prophylaxis—All HIV-exposed infants should receive zidovudine (also known as AZT) prophylaxis, started as soon after birth as possible and preferably within 6–12 hours of delivery. The usual dose (≥ 35 weeks gestational age) is 4 mg/kg orally twice daily and should be given for 6 weeks. Zidovudine dosing is different for preterm infants (< 35 weeks gestational age) (TABLE 4). Zidovudine can also be given intravenously for newborns initially unable to tolerate oral medications. In addition to zidovudine, newborns at high risk of perinatal infection – those whose mothers did not receive ARV drugs during pregnancy - should be given 3 oral doses of nevirapine beginning as soon as possible after birth (within 48 hours) (TABLE 4). These drugs are generally well tolerated by infants; anemia and neutropenia related to zidovudine are the most common adverse effects, and these usually resolve within several weeks after zidovudine discontinuation. Complete blood count with differential should be obtained at baseline; hematologic parameters should be reassessed at about age 4 weeks in infants with hematologic risk factors (such as prematurity or anemia at baseline) or clinical suspicion of anemia. Early discontinuation of infant ARV prophylaxis because of hematologic toxicity should be undertaken in consultation with a pediatric HIV expert.

In 2013, researchers reported an infant with well-documented perinatal HIV infection who received an ART treatment (not prophylaxis) regimen beginning at age 30 hours until shortly after age 1 year who had no evidence of HIV infection after the family discontinued her treatment. This case of apparent resolution of infection after early, intensive ARV treatment has sparked a great deal of interest in the potential for early, multi-drug therapy for high-risk newborns to result in functional cure. Until more evidence is available, this approach should be considered experimental and deviation from standard neonatal prophylaxis regimens should only be undertaken under the guidance of a pediatric HIV expert. The Perinatal HIV Hotline can also be helpful for providing guidance: http://www.nccc.ucsf.edu/

Routine HIV virologic testing schedule for HIV-exposed infants—Virologic testing (HIV DNA PCR or HIV RNA assays) should be performed within the first 14 to 21 days of life, at age 1 to 2 months, and then at age 4 to 6 months for all HIV-exposed infants. Many experts also perform a test in the newborn nursery, especially for high-risk infants (eg, whose mothers did not achieve virologic suppression by the time of delivery). Testing should never be performed on cord blood. HIV can be *presumptively* excluded (in non breastfed infants) on the basis of two negative virologic tests, both performed no earlier than age 14 days and at least one performed no earlier than age 1 month, or based on one negative virologic test performed no earlier than age 8 weeks. HIV can be *definitively* excluded on the basis of two negative virologic tests, both performed no earlier than age 1 month and at least one performed no earlier than age 4 months.

For infants whose mothers were diagnosed with HIV infection during breastfeeding, the recommended infant virologic testing schedule is baseline and then intervals of 4 to 6 weeks,

3 months, and 6 months after recognition of maternal infection and interruption of breastfeeding.

If, at any time, a virologic test is positive, the infant should be promptly recalled for confirmatory testing and assessment.

PCP prophylaxis and Immunizations

All infants with known or possible HIV infection, regardless of CD4 count or percentage, should be prescribed prophylaxis against PCP beginning at age 6 weeks. The preferred agent for prophylaxis is cotrimoxazole 2.5–5 mg (based on trimethoprim component)/kg body weight/dose given twice daily, usually on 3 days (consecutive or alternating) per week. Infants in whom HIV has been presumptively or definitively excluded by age 6 weeks do not need to start PCP prophylaxis; for infants who do not have virologic test results available by age 6 weeks, PCP prophylaxis should be started and then can be discontinued as soon as virologic testing results demonstrate presumptive or definitive absence of HIV infection.

HIV-exposed infants should receive all of standard immunizations in the first few months of life [20]. In fact, these infants may have lower levels of protective antibodies passively transferred from their HIV-infected mothers, putting them at higher risk of pneumococcal and other vaccine preventable diseases [24, 25]. While there is some theoretical concern about administering live rotavirus vaccine to infants with possible HIV infection, this vaccine is still generally recommended based on low likelihood that infants in the US will be HIV-infected and limited data demonstrating it is well tolerated in HIV-infected infants [26].

Importance of Primary care visits

Routine health maintenance visits for HIV-exposed infants offer the opportunity to detect growth faltering, abnormal neurodevelopment and physical exam findings (eg, candidiasis) that may signal the presence of HIV infection. These visits also permit clinicians to assess social support needs for mothers and families, review with parents/caretakers the testing and prophylaxis results and plans for the infant, and reinforce safe infant feeding recommendations. Feeding counseling messages should include complete avoidance of breastfeeding and advice that all HIV-infected adult caretakers should avoid pre-warming or pre-chewing food in their mouths before feeding it to their infants [27].

Long-term concerns for HIV-exposed uninfected infants

As a results of the use of ARV drugs and other prevention strategies, the vast majority of the approximately 9,000 infants born annually in the US to HIV-infected mothers [28] will escape HIV infection. Most ARV drugs have been used extensively enough in pregnancy to conclude there is little or no increased risk of congenital defects (though the potential teratogenicity of efavirenz continues to be debated [29]). But surveillance remains important as new ARV drugs and combinations will be used by pregnant women [30]. There is also evidence that use of combination ARV regimens in pregnancy – especially those that include protease inhibitors – may increase the risk of preterm birth and lower birthweight [31]. Longitudinal studies of perinatally ARV-exposed, HIV-uninfected children have been largely reassuring, but have raised some concerns about subtle ARV effects on hematologic

measures, immune function, growth, language and neurocognitive outcomes and effects in many organ systems [32–35]. In addition, children may experience long-term adverse effects of problems that are more common in HIV-affected families in the US (eg, poverty, mental illness, substance abuse) and of their mothers managing their HIV infection. Clinicians can assist mothers in deciding how and when to disclose their HIV infection to their older children and can encourage mothers to have advance care plans in place in case of sudden, severe illness.

Management of HIV Infection in Infants, Children and Adolescents

Patients who have positive HIV test results should be referred promptly to an HIV specialist for comprehensive evaluation (Table 5) so the clinical and immunologic stage of disease can be assessed and treatment recommended. The specialist group should be contacted as soon as the positive result is known, since immediate initiation of ART may be indicated, especially for infected infants and patients with advanced disease.

Baseline evaluation

Initial evaluation of an HIV-infected infant or child should include the mother's medical history, child's medical history, family history, and social history. A comprehensive physical examination should be performed and documented, including a developmental evaluation. Assessment of HIV-infected adolescent patients, as for all adolescents, should include a sexual history, substance use history, and sexual maturity staging.

Initial laboratory testing in an HIV-infected patient should include CD4 percentage and absolute cell counts, plasma quantitative HIV RNA concentration (viral load), HIV genotype to assess for baseline drug resistance mutations, complete blood count with differential count, serum chemistries with liver and renal function tests, a lipid profile, and urinalysis (TABLE 5). For children younger than 5 years of age, CD4 percentage is often used for monitoring immune status because the absolute CD4 cell count (number of CD4 cells/mm3) in this age group varies with age-related changes in absolute lymphocyte count. Screening for hepatitis B and C infection as well as for tuberculosis is recommended for all HIV-infected patients. In addition, sexually active adolescents should be screened for *Chlamydia* infection, gonorrhea, syphilis, and human papillomavirus infections. In contrast to the guidelines for cervical cancer screening in healthy women, cervical Papanicolaou smears are indicated routinely in all sexually active, HIV-infected adolescent girls, with colposcopy recommended for evaluation of abnormal results. Similarly, most experts perform anal Pap smears in HIV- infected adolescent men who have sex with men and HIV-infected sexually active women; anoscopy is recommended for evaluation of abnormal results.

HIV infection is a multisystem disease; clinical manifestations range from asymptomatic to complications affecting virtually every organ system (Table 1). The Centers for Disease Control and Prevention classification system designates clinical stages based on the patient's medical history and degree of immune suppression based on CD4 cell count or percentage (Tables 6 and 7). This information permits an estimated risk for future morbidity and mortality and provides a rationale for instituting specific opportunistic infection prophylaxis and initiating or deferring antiretroviral therapy.

Antiretroviral therapy: Goals and Principles

The goals of ART are to maximize the quality and longevity of life through: complete suppression of viral replication (goal of *non- detectable viral load)*; preservation or restoration of immunologic function (goal of *normal CD4 percentage or count);* and prevention of or improvement in clinical disease status (goal of *asymptomatic* state). Additional prevention goals for ART include PMTCT in pregnant women and reduction in sexual transmission for HIV-infected youth who have uninfected sexual partners.

The decision to start ART requires balancing of health benefits of HIV treatment with the potential adverse effects of ART and patient readiness to take daily medications. Based on clinical trial evidence demonstrating that prompt ART initiation in HIV-infected infants dramatically reduces risk of death and morbidity [36], ART is routinely recommended for all infants (age < 12 months). For both PMTCT and maternal health reasons, ART is also routinely recommended for all pregnant women. ART has generally been recommended for children (beyond infancy), adolescents and adults based on clinical stage of their HIV infection, level of CD4-defined immunodeficiency, and, to a lesser extent, plasma viral load (TABLE 8)[15a,36a]. Current US guidelines have moved to recommend ART for all adolescents and adults based on several factors: currently available ARV regimens are simpler, safer and highly potent; cohort studies suggest clinical benefits even at higher CD4 levels; and treating HIV-infected people dramatically reduces HIV transmission to sexual partners [37]. In fact, some experts advocate for intensive testing accompanied by immediate ART for those who test positive (the “test-and-treat” approach) as a way to contain the spread of HIV in communities and populations [38]. Since pre-adolescent children are not at risk of sexual transmission and have not been shown to benefit from ART at higher CD4 counts, current guidelines permit but do not strongly recommend ART for children who do not meet clinical and laboratory criteria.

The most common ART regimens include 2 nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) and one of the following: non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase inhibitor. The preferred and alternative initial ARV drug regimens vary by age, will be altered if baseline ARV drug resistance is detected, are updated frequently (see www.aidsinfo.gov), and should generally be prescribed by or in collaboration with an HIV specialist, so they will not be detailed here.

ART is generally composed of at least 3 ARV drugs from at least 2 different ARV drug classes. For older children and adults starting ART for the first time, most ARV regimen options can be given once daily, often as a single pill that is a coformulation of 3 ARV drugs. For infants and younger children, there are fewer ARV options, the regimen is given as separate ARV drugs, administration is at least twice daily, and some of the liquid formulations (especially lopinavir-ritonavir, Kaletra ®) have very poor palatability. For patients of all ages, ART efficacy depends on high levels of adherence to the regimen; as frequency of missed ARV doses increases, achieving ART goals becomes less likely and the emergence of drug resistance increases. For ARV drugs (such as efavirenz) in which a single point mutation in the viral genome results in complete drug resistance, resistance emerges quickly with poor adherence; for other drugs (such as most protease inhibitors) that require

multiple viral mutations to make the virus resistant, resistance emerges only after longer periods of non-adherence.

Planning treatment collaboratively with the patient and family strengthens the therapeutic relationship and promotes successful adherence and HIV control. Enlisting adult support in the home is beneficial regardless of the patient's age. Frequent clinical follow-up with viral load testing allows the clinician to identify problems early and help patients and families find successful solutions. Children starting a new ARV regimen should be evaluated in person or by phone within 1 to 2 weeks of starting ART to screen for adverse effects and to assess adherence. Many clinicians will plan additional contacts (in person or by telephone) with children and caregivers to support adherence during the first few weeks of therapy. Some clinicians also recommend an HIV RNA measurement within the initial weeks of therapy for early assessment of response/adherence to therapy. Patients generally achieve a undetectable viral load within 6 months, though suppression of extremely high viral loads in some infants may take several weeks longer. Failure to achieve undetectable viral load in this time frame strongly suggests suboptimal adherence rather than viral resistance to the ARV regimen. Immediate and intensive adherence counseling and support are warranted, since continued non-adherence can allow for development of drug resistance.

Once HIV infection is controlled on a stable regimen, most patients are seen every 3 to 4 months for routine monitoring of viral load, CD4 cell response, and clinical status, including evaluation for potential medication adverse effects or toxicities (TABLE 5). For patients having difficulty taking (eg, due to poor palatability) or tolerating (eg, adverse effects such as nausea or diarrhea) one ARV drug in the regimen, substitution of one new ARV drug can be effective. Patients who experience treatment failure with drug resistance will usually be offered a new regimen (change at least 2 of the ARV drugs) based on the resistance patterns and robust adherence counseling and support.

Drug-drug interactions between different ARV drugs as well as between ARV and non-ARV drugs (including non-prescription and herbal medicines) are common, complicated and potentially dangerous. Interactions can result in excessive toxicity or in loss of efficacy. As part of every clinical encounter – and especially when new drug will be prescribed – the patient's complete medication list should be reviewed and confirmed with the patient (and family); potential adverse drug interactions should be evaluated in collaboration with a pharmacist and/or through use of other available resources [39–41].

Prophylaxis & Immunizations for HIV-infected Infant, Children and Adolescents

Effective ART dramatically reduces the risk of opportunistic infections (OI) and improves the protective response elicited by many immunizations. However, regular assessment of need for OI prophylaxis and attention to recommended immunizations remain essential; guidelines for preventing and treating OIs, including immunization recommendations, are updated regularly (http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf)[20].

As part of every HIV monitoring visit, patients should be evaluated for indications for OI prophylaxis based on their immunologic (CD4) status, illness history and exposures. This is

especially important for infants, for all patients who have not yet started ART, and for patients in whom ART fails to result in virologic suppression (most commonly due to non-adherence).

PCP is one of the most common and deadly OIs. Cotrimoxazole is recommended for *all* HIV-exposed infants until HIV infection is presumptively or definitively excluded, for all HIV-infected infants until age 12 months, and for HIV-infected children and adolescents older than 1 year of age whose CD4 values fall into the severe immune suppression category. In addition, children who have had PCP should receive cotrimoxazole prophylaxis after PCP treatment, at least until they have sustained improvement of immunologic status on ART.

Mycobacterium avium complex (MAC) causes disease in patients with even more advanced immunosuppression than the threshold at which PCP occurs. Primary prevention of MAC with azithromycin or clarithromycin is thus recommended at lower CD4 values (≥6 years old with CD4 count <50 cells/mm3; ages 2 to <6 years with CD4 count of <75 cells/mm3; 1 to <2 years with CD4 count of <500 cells/mm3; <1 year old with CD4 count of <750 cells/mm3).

As part of every HIV monitoring visit, patients should be evaluated for indicated vaccines. While this recommendation seems common sense, studies have shown that HIV-infected children are at increased risk of not receiving recommended vaccines [42,43]. The recommended immunization schedule for HIV-infected children and youth is mostly the same as that for HIV-uninfected peers and is presented in Figures 1 and 2 of the OI guidelines [20] (http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf). There are, however, several important exceptions (TABLE 9).

While ART markedly reduces the risk of infections due to pneumococcus and other encapsulated bacteria, these infections continue to occur at higher rates in HIV-infected children. As a result, in addition to receiving the standard series of pneumococcal conjugate vaccine (PCV) in the first 2 years of life, HIV-infected children should also receive the 23-valent pneumococcal polysaccharide vaccine at age 2 years and then 3–5 years later. Furthermore, older children (6–18 years old) who never received PCV13 should receive one dose. Finally, children who are not fully vaccinated against *Hemophilus influenzae* type b (Hib) by age 5 years should receive a single dose of Hib conjugate vaccine.

HIV-infected children have been shown to be less likely to respond to some vaccines. Thus, they should receive a two-dose primary series of meningococcal conjugate vaccine (MCV) instead of a single dose. They should also have anti-hepatitis B surface antibody (HBsAb) measured 1–2 months after completing the HBV vaccine series to confirm a protective response.

Because of the potential for attenuated live vaccines to cause disease in immunocompromised hosts, use of live vaccines is either not recommended or limited to children without severe immune suppression. Limited data demonstrate that live-attenuated intranasal influenza vaccine (LAIV) is safe and immunogenic in HIV-infected children without severe immunosuppression [44], but, until more data are available, injectable

influenza vaccine rather than LAIV is recommended for all HIV-infected children. MMR and varicella vaccines are recommended for HIV-infected children who do not have evidence of severe immunosuppression. The combination MMR-V vaccine, however, should not be used as it contains a higher titer of varicella vaccine (than the monovalent varicella vaccine) and has not been studied in HIV-infected children.

Many people in the US with perinatal HIV infection received their MMR (and most other) vaccines as infants and young children, in an era before ART was available. Pre-ART responses to MMR are not as reliable or durable as responses in HIV-infected children receiving ART. Based on evidence that high proportions of US youth with perinatal HIV infection lack immunity to measles, mumps and rubella and evidence that reimmunization is effective in those who were not immune when MMR vaccination preceded ART, it is recommended that individuals with perinatal HIV infection who were vaccinated prior to effective ART should receive 2 appropriately spaced doses of MMR vaccine doses once effective cART has been established, unless they have other acceptable current evidence of measles, rubella, and mumps immunity.

Complications of HIV infection in the cART era

With effective cART, HIV-infected children experience much lower rates of serious illness, can participate in the same activities as their peers, and expect to live long and relatively healthy lives. Whether life expectancy with treated perinatal HIV infection will be the same as that for people without perinatal HIV infection is unknown, since the oldest people with perinatal infection are just reaching their 30s.

The pattern of OIs and other illnesses that were typical of untreated HIV infection (TABLE 1) is uncommon today, though these problems continue to occur in children with unrecognized HIV infection and in children – and especially adolescents -who are not able to take cART reliably. The spectrum of problems seen in children and youth receiving effective cART includes complications of chronic HIV infection itself as well as residual effects of problems that occurred before cART was initiated, adverse effects of ARV drugs, and comorbidities that are more common in US communities burdened by poverty, mental illness and substance abuse where perinatal HIV infection is most likely to occur (TABLE).

Counseling and Support

Coping With the Diagnosis and Prognosis

Learning of a new diagnosis of HIV infection for oneself or one’s child is emotionally devastating for most people. While providing a listening ear and emotional support, clinicians also can offer hope and reassurance about the availability of effective treatment that can result in improved quality of life and survival for people living with HIV infection in the United States.

Disclosure of HIV Infection Status

HIV infection remains a stigmatizing diagnosis. Ignorance, misinformation, and fear in families and communities cause people living with HIV infection to keep their status a

secret. However, this practice has negative consequences, such as isolating the HIV-positive individual from social support and risking additional spread of HIV to sexual partners. Planned disclosure to family members and friends can increase practical and emotional support for the HIV-positive person. Sexual partners can make informed decisions about how to protect themselves from exposure to HIV.

In contrast to adolescents and adults, disclosure of HIV status to children should be undertaken over time, providing sequential pieces of practical health information that match the developmental capacity of the child. This process builds a strong foundation for children to participate meaningfully in their HIV care. Most perinatally infected children learn of their HIV diagnosis by name between ages 8 and 10 years.

Adherence to Care and Treatment

Most people do not adhere to the treatment recommendations of their health-care practitioners all of the time. Infants and young children depend upon their adult caretakers for adherence. Developmentally normal behaviors and stages (eg, toddlers and adolescents) can make adherence to medications especially difficult.

Poor adherence leads to poor health outcomes in many diseases such as asthma and diabetes. However, HIV treatment demands very high levels of adherence to drug regimens to avoid the development of viral resistance and the loss of future efficacy of anti-HIV drugs. The need for intensive education and support for children and adolescents living with HIV infection cannot be overstated.

School and Sports Participation

Children and adolescents who have HIV infection can participate fully in the educational and extracurricular activities in school. There is no obligation to notify school personnel of a student's HIV infection status. Any sport may be played if the student's health status allows. For all athletes, regardless of HIV infection status, skin lesions should be covered properly, and athletic personnel should use standard precautions when handling blood or body fluids that have visible blood. Certain high-contact sports (such as wrestling and boxing) may create a situation that favors viral transmission (likely bleeding plus skin breaks). Some experts advise athletes who have a detectable viral load to avoid such high- contact sports.

Transition to Adult Health Care

Children born with HIV infection in the United States during the 1980s are now young adults. They continue to be the pioneers who challenge our assumptions and identify unmet needs for care and support services. There is a pressing need to develop and implement programs to transition youth successfully to adult HIV health-care clinicians [45]. Practical concerns such as transmitting a complete and coherent medical record and psychological concerns such as the loss of long-term supportive relationships must be addressed.

Abbreviations

HIV	Human Immunodeficiency Virus

AIDS	Acquired Immunodeficiency Syndrome
PMTCT	prevention of maternal-to-child transmission
ARV	antiretroviral
ART	ARV therapy
cART	combination ARV therapy
WHO	World Health Organization
ACTG	AIDS Clinical Trials Group
CDC	Centers for Disease Control and Prevention
USPSTF	U.S. Preventive Services Task Force
AAP	American Academy of Pediatrics
MSM	men who have sex with men
STI	sexually transmitted infection
PCP	Pneumocystis pneumonia
LIP	lymphocytic interstitial pneumonitis
TB	tuberculosis
EIA	enzyme-linked immunoassay
WB	Western blot
IFA	Immunofluorescent assay
PCR	polymerase chain reaction
ZDV	zidovudine
NVP	nevirapine
NRTI	nucleoside (or nucleotide) reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
MAC	*Mycobacterium avium* complex
OI	opportunistic infection
PCV	pneumococcal conjugate vaccine
Hib	*Hemophilus influenzae* type b
MCV	meningococcal conjugate vaccine
HBsAb	anti-hepatitis B surface antibody
LAIV	live-attenuated intranasal influenza vaccine
MMR	measles-mumps-rubella vaccine

MMR-V	measles-mumps-rubella-varicella vaccine
VL	viral load

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TABLE 1

Relative Frequency of Clinical Conditions in Untreated HIV Infection (from Simpkins et al, Pediatrics in Review, 2009) [46]

		Relative Frequency	
Body System or Illness Category*	**Specific Conditions**	**Common**	**Uncommon**
Infections: recurrent, severe, or unusual (opportunistic)	Recurrent or chronic otitis, sinusitis	C	
	Recurrent or severe pneumonia	C	
	Recurrent or severe bacteremia	C	
	Opportunistic infections, such as PCP, MAC, invasive candidal infections	C	
Lymphoreticular system	Generalized lymphadenopathy	C	
	Hepatomegaly	C	
	Splenomegaly	C	
	Parotid enlargement	C	
	Lymphoid interstitial pneumonitis	C	
Growth	Failure to thrive	C	
	Weight loss, wasting	C	
	Stunting	C	
	Delayed puberty	C	
Neurologic	Neurodevelopmental delay or regression	C	
	Abnormal tone (increased or decreased)	C	
	Gait disturbance	C	
	Peripheral neuropathy		U
	Stroke		U
Pulmonary	Bacterial pneumonia	C	
	Lymphoid interstitial pneumonitis	C	
	Bronchiectasis		U
	Pneumothorax		U
Cardiovascular	Cardiomyopathy		U
	Pericardial effusion		U
	Conduction abnormalities		U
	Hypertension		U
	Vasculopathy		U
Gastrointestinal	Gastritis	C	
	Duodenitis	C	
	Hepatitis		U
	Pancreatitis		U
	Cholecystitis		U
	Diarrhea	C	
	Gastrointestinal bleeding		U

Body System or Illness Category*	Specific Conditions	Relative Frequency	
		Common	Uncommon
	Abdominal pain	C	
Renal	Proteinuria	C	
	Renal tubular acidosis		U
	Renal failure		U
	Hypertension		U
Hematologic	Anemia	C	
	Neutropenia	C	
	Thrombocytopenia	C	
Dermatologic	Seborrhea	C	
	Eczema	C	
	Urticaria		U
	Zoster	C	
	Herpes simplex infections	C	
	Tinea corporis, capitis, unguium	C	
	Bacterial infections	C	
	Molluscum contagiosum	C	
	Warts (HPV)	C	
Genital/Reproductive	HPV-related dysplasia (cervical, anal)	C	
	Pelvic inflammatory disease	C	
	Delayed puberty	C	

*Some conditions belong to more than one category. HPV=human papillomavirus, MAC=*Mycobacterium avium* complex, PCP=*Pneumocystis jiroveci* pneumonia

TABLE 2

Presentation of acute HIV infection [Adapted from Ref. 21]

Sign or symptom	Frequency (%)
Fever	53–90
Weight loss/anorexia	46–76
Fatigue	26–90
GI upset	31–68
Rash	9–80
Headache	32–70
Lymphadenopathy	7–75
Pharyngitis	15–70
Myalgia or arthralgia	18–70
Aseptic meningitis	24
Oral ulcers	10–20
Leukopenia	40

TABLE 3

Diagnostic Assays Used for HIV Testing

1) HIV antibody tests

- Enzyme-linked immunoassays (EIA), Western blot (WB), Immunofluorescent Assays (IFA).
- Rapid EIA assays available; can be performed on blood or saliva specimen.
- Traditional HIV antibody testing has required positive EIA test, confirmed by positive WB (or IFA) for HIV diagnosis

2) HIV antigen/antibody ("4th generation") tests

- Detects anti-HIV IgM and IgG antibodies and p24 antigen
- IgM and antigen detection components improve sensitivity for detecting primary HIV infection
- Not appropriate for HIV diagnosis in infants (< 18 months old)

3) Nucleic Acid Amplification Tests

- HIV DNA polymerase chain reaction (PCR); used only for infant diagnosis
- HIV RNA PCR and other assays; quantitative and qualitative; used for infant diagnosis and primary HIV infection diagnosis. (Quantitative assays also used for monitoring virologic response to antiretroviral therapy.)

See http://www.cdc.gov/hiv/pdf/policies_Draft_HIV_Testing_Alg_Rec_508.2.pdf [23] for additional information.

TABLE 4

Neonatal Antiretroviral (ARV) Drug Dosing for Prevention of Mother-to-Child Transmission of HIV

ARV Drug	Dosing	Duration
Zidovudine (ZDV) should be given to ALL HIV-exposed newborns and should be started as soon after birth as possible, preferably within 6–12 hours of delivery		
ZDV	**≥35 weeks' gestation at birth**: 4 mg/kg/dose PO twice daily (if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 hours of delivery, then every 12 hours)	Birth through 6 weeks
ZDV	**≥30 to <35 weeks' gestation at birth**: 2 mg/kg/dose PO (or 1.5 mg/kg/dose IV) every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours at age 15 days	Birth through 6 weeks
ZDV	**<30 weeks' gestation at birth**: 2 mg/kg body weight/dose PO (or 1.5 mg/kg/dose IV) every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours after age 4 weeks	Birth through 6 weeks
Nevirapine (NVP) administered in addition to ZDV to Newborns of HIV-infected Women who Received No Antepartum ARV Prophylaxis		
Nevirapine (NVP)	**Weight Band dosing** **Birth weight 1.5–2 kg: 8 mg* for each dose** **Birth weight >2 kg: 12 mg* for each dose** **(*NOTE: NVP dosing given as actual doses, NOT as mg/kg dosing)**	3 doses in the first week of life • 1st dose within 48 hours of birth (as soon after birth as possible) • 2nd dose 48 hours after 1st • 3rd dose 96 hours after 2nd

Adapted from: http://www.aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0 [11]

Table 5

Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (Adapted from http://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv-guidelines/77/monitoring-of-children-on-antiretroviral-therapy)[15a]

	Diagnosis/Baseline	ART Initiation	1–2 Weeks on Therapy	4–8 Weeks on Therapy	Every 3–4 Months[1]	Every 6–12 Months
Clinical History/Physical Exam	X	X	X	X	X	X
CBC w/Differential	X	X		X	X	
Electrolytes, Glucose, BUN, Creatinine, Bilirubin	X	X			X	
AST/ALT	X	X	X[2]	X[2]	X	
Albumin, Total Protein, Calcium, Phosphate	X	X				X
CD4 Count/%	X	X		X[3]	X	
HIV RNA (viral load)	X	X	X	X	X	
Drug Resistance Testing	X					
Adherence Evaluation		X	X	X	X	
Lipid Panel	X	X				X
Urinalysis	X	X				X

[1] For children who are on stable ART, many clinicians consider 6-month intervals between monitoring lab tests.

[2] In children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.

[3] Some clinicians do not recommend a CD4 cell count/percentage at this time, considering it too early to expect an immunologic response.

TABLE 6

CD4 T-lymphocyte-Based Assessment of Degree of Immunosuppression in HIV Infection

Age Group	No immunosuppression		Moderate immunosuppression		Severe immunosuppression	
	CD4 count	CD4 %	CD4 count	CD4 %	CD4 count	CD4 %
< 12 months	≥ 1500	≥ 34%	750 to < 1500	26 to < 34%	< 750	< 26%
1 to < 6 years	≥ 1000	≥ 30%	500 to < 1000	22 to < 30%	< 500	< 22%
≥ 6 years	≥ 500	≥ 26%	200 to < 500	14 to < 26%	< 200	< 14%

Ref. 39

TABLE 7

Clinical Staging of HIV Infection [47]

HIV Stage	Definition	Comment
1	No immunosuppression (based on CD4 values) *and* No history of AIDS-defining illness	
2	Moderate immunosuppression (based on CD4 values) *and* No history of AIDS-defining illness	
3	Severe immunosuppression (based on CD4 values) *or* History of AIDS-defining illness	

TABLE 8

Summary of Recommendations for Starting ART [15a,36a]

Population	CD4	HIV Clinical Illness Severity	Recommendation
Infants (< 12 months old	ANY	ANY	TREAT ALL
1 to <3 years old	<1,000 or < 25%	Moderate or Severe	• TREAT for CD4 or Clinical criteria. • Otherwise CONSIDER treatment, especially if VL > 100,000 copies/mL
3 to < 5 years old	< 750 or < 25%	Moderate or Severe	• TREAT for CD4 or Clinical criteria. • Otherwise CONSIDER treatment, especially if VL > 100,000 copies/mL
≥ 5 years old	< 500	Moderate or Severe	• TREAT for CD4 or Clinical criteria. • Otherwise (1) CONSIDER treatment for children, especially if VL > 100,000 copies/mL; (2) TREAT all adolescents/adults.
Pregnant women	ANY	ANY	TREAT ALL

TABLE 9

Summary of How Immunization Recommendations for HIV-infected Children Differ from Standard Immunization Schedule

Vaccine	Specific recommendations for HIV-infected children	Rationale for specialized recommendation in HIV-infected children
PCV13	Administer to 6–18 year-olds who have not received it	Elevated risk of pneumococcal infections
PPS23	Administer 2-dose series beginning at age 2 years	Elevated risk of pneumococcal infections
Hib	Administer one dose Hib vaccine to children ≥ 5 years if incomplete Hib vaccine history	Elevated risk of infections due to encapsulated bacteria
MCV	Primary series should be 2 doses at least 8 weeks apart	Lower response rate to single dose of MCV
HBV	Routine assessment of seroprotection (anti-HBsAb ≥10 mIU/mL) 1–2 months after completion of series	Lower response rate to vaccine series
Influenza	Use trivalent injectable vaccine instead of live-attenuated intranasal vaccine	Potential for live vaccines to cause illness in immunocompromised host
Varicella	Do not administer if severely immunocompromised or severe symptoms	Potential for live vaccines to cause illness in immunocompromised host
MMR-V	Do not use. * MMR-V has higher varicella vaccine dose than monovalent varicella vaccine	Potential for live vaccines to cause illness in immunocompromised host.*
MMR	Do not administer if severely immunocompromised.	Potential for live vaccines to cause illness in immunocompromised host
	Repeat MMR immunization (once receiving effective ART) if MMR doses given before effective ART established.	Lower probability and less durability of MMR vaccine response before ART

TABLE 10

Complications and Problems in Perinatally Infected Children and Youth Receiving Effective cART [49]

Body System	Problem/Complication	Description
Neurocognitive	Learning/cognitive impairment, attention disorders, behavioral problems and mental illness	Common, likely multifactorial.
Neurologic	Peripheral neuropathy	Was more common with certain drugs (stavudine, didanosine) no longer commonly used.
	Static encephalopathy	Residual effects of encephalopathy and/or strokes that occurred before effective cART
Growth & Nutrition	Short stature	Early cART improves growth but cannot fully correct years of poor linear growth if effective cART started late.
	Lipoatrophy	Subcutaneous fat loss in face, extremities, and buttocks; especially related to stavudine use. May not normalize after stavudine discontinued.
	Lipohypertrophy	Excessive central fat deposition in abdomen, breasts, dorsocervical “buffalo hump”. May be related to HIV and/or to certain ARVs.
Cardiovascular risk factors	Dyslipidemia, insulin resistance	Especially related to ARV drugs (protease inhibitors, some NRTIs)
	Chronic inflammation	Evidence of persistent multifactorial inflammation and immune activation despite early and prolonged effective cART.
Pulmonary	Chronic lung disease	Bronchiectasis and other chronic lung changes from precART LIP and repeated infections.
	Asthma	May be related to incomplete immune system normalization despite effective cART
Renal	Renal failure	Frank renal failure uncommon with cART; ARV-related tubulopathy and glomerulopathy; multifactorial progressive loss of renal function.
Hepatic	Liver inflammation/damage	Related to ARV, concomitant viral hepatitis
Bone	Low bone mineral density; Bone fragility	Multifactorial including certain ARVs (Tenofovir) and traditional (nonHIV) risk factors for poor bone health
Reproductive health	Anogenital HPV-related dysplasia/malignancy	Not clear how much this risk is attenuated by effective cART
Malignancy	Overall higher rate	
Hematologic	Anemia	Multifactorial including ARV related (zidovudine)
	Neutropenia	Multifactorial including ARV related (zidovudine)
Mitochondrial function	Lactic acidosis and other manifestations	Thought due to inhibition of mitochondrial DNA synthesis, especially by stavudine and didanosine. Manifestations highly variable: asymptomatic lactate elevation; fatigue, weakness, myalgias, abdominal pain, and dyspnea; to severe multi-organ involvement. Implicated in peripheral neuropathy, cardiomyopathy, and neurotoxicity.

See Chapter 113, Siberry GK and Hazra R. Management of HIV Infection, in *Principles and Practice of Pediatric Infectious Diseases*, 4th ed., Long SS, Pickering LK and Prober CG, eds. Elsevier Saunders, 2011, Philadelphia.