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

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Practice Gap

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

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 patients infected with and affected by human immunodeficiency virus (HIV).
2. Understand the epidemiology of HIV 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.

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ABBREVIATIONS

ART	antiretroviral therapy
ARV	antiretroviral
cART	combination antiretroviral therapy
CDC	Centers for Disease Control and Prevention
EIA	enzyme-linked immunoassay
HIV	human immunodeficiency virus
MAC	*Mycobacterium avium* complex
MMR	measles-mumps-rubella
MSM	men who have sex with men
MTCT	maternal-to-child transmission
OI	opportunistic infection
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
STI	sexually transmitted infection

Since the first description of infants with human immunodeficiency virus (HIV) infection in the early 1980s, (1)(2) tremendous advances have been made 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% to 2% in the United States, and the World Health Organization 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 markedly 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 (approximately 10%) are younger than 15 years. (4) Nearly all (95%) children younger than 15 years acquired HIV infection perinatally; in fact, a substantial number of the 2 million adolescents (ages 10-19 years) 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 (ages <15 years) had perinatal HIV infection, but this number represents approximately half of all perinatally infected HIV-infected people in the United States because 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)(6)(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 nonbreastfeeding populations, 25% to 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 (MSM). 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-1 and HIV-2 are enveloped, single-strand RNA retroviruses. HIV-1 is overwhelmingly responsible for HIV infections worldwide, including the United States. 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 or macrophages. HIV binds the CD4 target 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 caesarean section for HIV-infected women who reach term without achieving plasma HIV virologic suppression, and providing replacement feeding instead of breast milk 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 ARV drugs to mothers or infants during breastfeeding has become an effective means to allow breastfeeding while reducing the risk of HIV transmission. In the United States, 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 breast milk HIV transmission (residual transmission can be as high as 5%) and safe and affordable replacement feeding is available. (11)(12)

The ability of ARV drugs to prevent MTCT was first found in the landmark AIDS Clinical Trials Group 076 trial, which found that zidovudine administered during pregnancy,

intrapartum, and (to the infant) after birth could cut transmission from 26% to 8% in the absence of breastfeeding. (13) Subsequent studies found even greater efficacy for combination ARV therapy (cART), which was generally composed of at least 3 ARV drugs from at least 2 different classes. Routine use of cART for pregnant women in the United States has resulted in MTCT risk less than 1% to 2% and estimated annual new infant infections numbering about 200 nationwide. (14) In fact, pregnant women who achieve consistent plasma HIV virologic suppression during pregnancy are at such low risk of MTCT that neither elective caesarean section nor intrapartum ARV therapy (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 receiving cART during pregnancy, and incident HIV infection in pregnant and breastfeeding women remain important problems that contribute to residual infant infections in the United States. (14)(15)

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. 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) less than 1000 copies/mL by the end of pregnancy, 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 during 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, or sexually transmitted infection (STI) diagnosis signs or 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 1 diagnosed HIV case per 1,000 pregnant women per year. (16)(17) 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 and infant ARV therapy should be initiated, pending the confirmatory test result. If the confirmatory HIV test result is positive, infant ARV therapy should be continued; if the test result is negative, then infant ARV therapy should be stopped.

Newborn nurseries should have procedures in place to alert nursery staff when an HIV-exposed infant is born because neonatal ARV prophylaxis should be initiated as soon after birth as possible, ideally within 6 to 12 hours (see the Management of HIV-Exposed Infant section). On 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 a rapid maternal or infant antibody test result is positive, the infant should initiate ARV therapy immediately, pending confirmatory testing, as for women with positive rapid antibody test results during labor and delivery (see above).

RECOGNIZING HIV INFECTION IN INFANTS, CHILDREN, AND ADOLESCENTS: ROUTINE TESTING AND CLINICAL PRESENTATIONS

HIV infection should be suspected in patients who present with typical clinical findings, but many children and youth have their conditions 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 the Management of HIV-Exposed Infant section). If the maternal HIV status has not been determined, maternal HIV antibody testing (or, if the mother is not available, infant HIV antibody testing) should be requested to determine whether the infant is HIV exposed.

Many new US cases of HIV infection are diagnosed in infants and children born outside the United States, especially in high HIV prevalence settings, such as sub-Saharan Africa. (18) Some of these children have come to the United States with their mothers or families, whereas 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 age ≥18 months) or for perinatal exposure (in those age <18 months); those younger than 18 months who are HIV antibody positive will require additional HIV virologic testing, as for HIV-exposed newborns, to assess whether they are HIV infected (see the HIV Testing in Infants, Children, and Adolescents section).

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. Although 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

The Centers for Disease Control and Prevention (CDC) recommends performing an HIV test routinely beginning at age 13 years, the US Preventive Services Task Force guidelines recommend routine screening beginning at age 15 years, and the American Academy of Pediatrics recommends HIV testing at least once by age 16 to 18 years in patient populations with HIV prevalence of 0.1% or higher. (16)(19)(20) 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, whereas an interval of 3 to 5 years is reasonable for those at elevated but lesser degree of risk. (16) Important indicators of very high risk include young 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 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. Although full implementation of prevention of MTCT 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. (22) Rare in the first month of life, this condition peaks at ages 3 to 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. (22)

Mucosal candidiasis is a common and early sign of HIV infection in untreated infants. Although 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 that cause immunodeficiency.

Recurrent bacterial pneumonia and other bacterial infections (sinusitis and otitis) were common in HIV-infected infants and children before cART and may be the first clue to unrecognized HIV infection. Although 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) 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 tuberculosis disease, increasing the risk of tuberculosis infection in children in their households. HIV-infected children who acquire tuberculosis

TABLE 1. **Relative Frequency of Clinical Conditions in Untreated Human Immunodeficiency Virus Infection**

SPECIFIC CONDITIONS IN BODY SYSTEM OR ILLNESS CATEGORY[a]	RELATIVE FREQUENCY
Infections: recurrent, severe, or unusual (opportunistic)	
Recurrent or chronic otitis, sinusitis	Common
Recurrent or severe pneumonia	Common
Recurrent or severe bacteremia	Common
Opportunistic infections, such as PCP, MAC, invasive candidal infections	Common
Lymphoreticular system	
Generalized lymphadenopathy	Common
Hepatomegaly	Common
Splenomegaly	Common
Parotid enlargement	Common
Lymphoid interstitial pneumonitis	Common
Growth	
Failure to thrive	Common
Weight loss, wasting	Common
Stunting	Common
Delayed puberty	Common
Neurologic	
Neurodevelopmental delay or regression	Common
Abnormal tone (increased or decreased)	Common
Gait disturbance	Common
Peripheral neuropathy	Uncommon
Stroke	Uncommon
Pulmonary	
Bacterial pneumonia	Common
Lymphoid interstitial pneumonitis	Common
Bronchiectasis	Uncommon
Pneumothorax	Uncommon
Cardiovascular	
Cardiomyopathy	Uncommon
Pericardial effusion	Uncommon
Conduction abnormalities	Uncommon
Hypertension	Uncommon
Vasculopathy	Uncommon
Gastrointestinal	
Gastritis	Common

Continued

TABLE 1. (Continued)

SPECIFIC CONDITIONS IN BODY SYSTEM OR ILLNESS CATEGORY[a]	RELATIVE FREQUENCY
Duodenitis	Common
Hepatitis	Uncommon
Pancreatitis	Uncommon
Cholecystitis	Uncommon
Diarrhea	Common
Gastrointestinal bleeding	Uncommon
Abdominal pain	Common
Renal	
Proteinuria	Common
Renal tubular acidosis	Uncommon
Renal failure	Uncommon
Hypertension	Uncommon
Hematologic	
Anemia	Common
Neutropenia	Common
Thrombocytopenia	Common
Dermatologic	
Seborrhea	Common
Eczema	Common
Urticaria	Uncommon
Zoster	Common
Herpes simplex infections	Common
Tinea corporis, capitis, unguium	Common
Bacterial infections	Common
Molluscum contagiosum	Common
Warts (HPV)	Common
Genital or reproductive	
HPV-related dysplasia (cervical, anal)	Common
Pelvic inflammatory disease	Common
Delayed puberty	Common

HPV=human papillomavirus, MAC=Mycobacterium avium *complex, PCP*=Pneumocystis jiroveci *pneumonia.*
[a]*Some conditions belong to more than one category.*
Adapted from Simpkins et al. (21)

infection are then more likely to develop tuberculosis 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 United States, 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 merits thorough review of the child's history of other illnesses, careful physical examination, and ascertainment of health status of mother and siblings to determine whether 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 several days to weeks after incident HIV infection when HIV viremia (and potential for transmission to others) is high and HIV antibodies have not yet appeared. Most episodes (50%-90%) of primary HIV infection are symptomatic, but the variable severity and nonspecific flulike 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. (23) 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. Because this early phase of HIV infection precedes the full antibody response, patients with suspected acute HIV infection should be tested with a fourth-generation combined antigen-antibody test or a plasma HIV RNA test (see the HIV Testing Assays section). Patients diagnosed as having 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 therapy 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.

TABLE 2. **Presentation of Acute Human Immunodeficiency Virus Infection**

SIGN OR SYMPTOM	FREQUENCY, %
Fever	53–90
Weight loss or anorexia	46–76
Fatigue	26–90
Gastrointestinal 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

Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Richey LE, Alperin J. Acute human immunodeficiency virus infection. Am J Med Sci. *2013:345(2):136–142. (24)*

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. (16) HIV testing provides an important opportunity to educate 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 by the CDC. Clinicians should be familiar with their local laws and regulations because some jurisdictions and institutions continue to require such counseling and/or written consent to proceed with testing. (25) 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 (age ≥18 months), adolescents, and adults (including pregnant women) relies on detection of HIV antibody in a blood specimen in 2 steps: a screening enzyme-linked immunoassay (EIA) is performed first, and if the result is reactive, a confirmatory HIV antibody test, such as a Western blot, is then performed. Both tests must be positive to meet the criteria for HIV infection. Rapid, point-of-care EIAs are available for detecting HIV antibodies in blood and saliva specimens; negative results reliably exclude established HIV infection and standard EIA tests (none is sensitive for detecting acute HIV infection), but positive test results need to be confirmed with standard HIV diagnostic assays.

Newer fourth-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. (26) The CDC is anticipated to update their guidelines to recommend use of these fourth-generation assays as the preferred initial test to screen for HIV infection (for those at least age 18 months), 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 fourth-generation combined 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 recent or primary HIV infection, when viremia is present but antibody is not, and 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, although the DNA PCR or RNA assays are equally acceptable for this purpose. Combined antigen-antibody assays should not be used for infant diagnosis. HIV RNA assays and combined antigen-antibody assays are both appropriate for detecting primary HIV infection (beyond age 18 months). 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.

TABLE 3. **Diagnostic Assays Used for HIV Testing**

HIV antibody tests
EIAs, WB , IFAs
Rapid EIAs available; can be performed on blood or saliva specimen
Traditional HIV antibody testing has required positive EIA result, confirmed by positive WB (or IFA) result for HIV diagnosis
Combination HIV antigen and antibody (fourth-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 (age <18 months)
Nucleic acid amplification tests
HIV DNA 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)

EIA=enzyme immunoassay; HIV=human immunodeficiency virus; IFA=immunofluorescent assay; PCR=polymerase chain reaction; WB=Western blot.
See Centers for Disease Control and Prevention (26) for additional information.

MANAGEMENT OF HIV-EXPOSED INFANTS

Primary medical care practitioners 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 the need for PCP prophylaxis, routine immunizations, monitoring for manifestations of HIV infection, and reinforcing education and counseling for the mother and 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 prophylaxis, started as soon after birth as possible and preferably within 6 to 12 hours of delivery. The usual dose (gestational

age ≥35 weeks) is 4 mg/kg orally twice daily and should be given for 6 weeks. Zidovudine dosing is different for preterm infants (gestational age <35 weeks) (Table 4). Zidovudine can also be given intravenously (at a different dose) 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 conditions usually resolve within several weeks after discontinuation of zidovudine therapy. Complete blood cell count with differential should be measured at baseline; hematologic parameters should be reassessed at approximately 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 toxic effects should be undertaken in consultation with a pediatric HIV expert.

In 2013, researchers described 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, multidrug 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

TABLE 4. **Neonatal ARV Drug Dosing for Prevention of Mother-to-Child Transmission of HIV**

ARV DRUG AND DOSE	DURATION
Zidovudine 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	
≥35 weeks' gestation at birth: 4 mg/kg orally twice daily (if unable to tolerate oral agents, 3 mg/kg/dose intravenously, beginning within 6–12 hours of delivery, then every 12 hours)	Birth through 6 weeks
≥30 to <35 weeks' gestation at birth: 2 mg/kg orally (or 1.5 mg/kg intravenously) every 12 hours, advanced to 3 mg/kg orally (or 2.3 mg/kg intravenously) every 12 hours at age 15 days	Birth through 6 weeks
<30 weeks' gestation at birth: 2 mg/kg orally (or 1.5 mg/kg intravenously) every 12 hours, advanced to 3 mg/kg orally (or 2.3 mg/kg intravenously) every 12 hours after age 4 weeks	Birth through 6 weeks
Nevirapine administered in addition to zidovudine to newborns of HIV-infected women who received no antepartum ARV prophylaxis	
Weight band dosing	Three doses in the first week of life
Birth weight 1.5–2 kg: 8 mg for each dose[a]	First dose within 48 hours of birth (as soon after birth as possible)
Birth weight >2 kg: 12 mg for each dose[a]	Second dose 48 hours after first
	Third dose 96 hours after second

ARV=antiretroviral; HIV=human immunodeficiency virus.
Adapted from AIDS Info. (11)
[a]*Nevirapine dosing given as actual doses not as milligram per kilogram dosing.*

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 nonbreastfed infants) on the basis of 2 negative results on virologic tests performed no earlier than age 14 days and at least 1 performed no earlier than age 1 month or based on 1 negative result on a virologic test performed no earlier than age 8 weeks. HIV can be *definitively* excluded on the basis of 2 negative results on virologic tests both performed no earlier than age 1 month and at least 1 performed no earlier than age 4 months.

For infants whose mothers were diagnosed as having 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 result 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 cell count or percentage, should be prescribed PCP prophylaxis beginning at age 6 weeks. The preferred agent for prophylaxis is 2.5 to 5 mg/kg of cotrimoxazole (based on trimethoprim component) per 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. (23) 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. (27)(28) Although 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 United States will be HIV infected and limited data demonstrating it is well tolerated in HIV-infected infants. (29)

Importance of Primary Care Visits

Routine health maintenance visits for HIV-exposed infants offer the opportunity to detect growth faltering, abnormal neurodevelopment, and physical examination 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 and 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 prewarming or prechewing food in their mouths before feeding it to their infants. (30)

Long-Term Concerns for HIV-Exposed Uninfected Infants

As a result of the use of ARV drugs and other prevention strategies, most of the approximately 9,000 infants born annually in the United States to HIV-infected mothers (31) 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 (although the potential teratogenicity of efavirenz continues to be debated). (32) However, surveillance remains important because new ARV drugs and combinations will be used by pregnant women. (33) 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 birth weight. (34) 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. (35)(36)(37)(38) In addition, children may experience long-term adverse effects of problems that are more common in HIV-affected families in the United States (eg, poverty, mental illness, and 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 because immediate initiation of ART may be indicated, especially for infected infants and patients with advanced disease.

TABLE 5. **Clinical and Laboratory Monitoring of Children Before and After Initiation of ART**

	DIAGNOSIS/ BASELINE	ART INITIATION	1–2 WEEKS OF THERAPY	4–8 WEEKS OF THERAPY	EVERY 3–4 MONTHS[a]	EVERY 6–12 MONTHS
Clinical history and physical examination	X	X	X	X	X	X
CBC count with differential	X	X		X	X	
Electrolytes, glucose, BUN, creatinine, bilirubin	X	X			X	
AST and ALT	X	X	X[b]	X[b]	X	
Albumin, total protein, calcium, phosphate	X	X				X
CD4 cell count or percentage	X	X		X[c]	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

ALT=alanine aminotransferase; ART=antiretroviral therapy; AST=aspartate aminotransferase; CBC=complete blood cell; HIV=human immunodeficiency virus.

Adapted from Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. (17)

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

[b]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.

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

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 cell count with differential, serum chemical analyses with liver and renal function tests, a lipid profile, and urinalysis (Table 5). For children younger than 5 years old, CD4 percentage is often used for monitoring immune status because the absolute CD4 cell count in this age group varies with age-related changes in absolute lymphocyte count. Screening for hepatitis B and C infection and 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 Papanicolaou smears in HIV-infected adolescent MSM 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 that affect virtually every organ system (Table 1). The CDC classification system designates clinical stages based on the patient's medical history and degree of immunosuppression based on CD4 cell count or percentage (Table 6 and Table 7). This information permits an estimated risk of future morbidity and mortality and provides a rationale for instituting specific opportunistic infection (OI) prophylaxis and initiating or deferring ART.

ART: Goals and Principles

The goals of ART are to maximize the quality and longevity of life through complete suppression of viral replication (goal of nondetectable viral load), preservation or restoration of immunologic function (goal of normal CD4 cell count or percentage), and prevention of or improvement in clinical disease status (goal of asymptomatic state). Additional prevention goals for ART include prevention of MTCT 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. On the basis of clinical trial evidence indicating that prompt ART initiation in HIV-infected infants markedly reduces risk of death and morbidity, (41) ART is routinely recommended for all infants (age <12 months). For both prevention of MTCT 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). (17)(42) 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 markedly reduces HIV transmission to sexual partners. (43) 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. (44) Because preadolescent children are not at risk of sexual transmission and have not been found to benefit from ART at higher CD4 cell 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 and one of the following: nonnucleoside reverse transcriptase inhibitor, protease inhibitor, 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) have 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 nonadherence.

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 telephone within 1 to 2 weeks of starting ART to screen for adverse effects and to assess adherence. Many

TABLE 6. **CD4 T-Lymphocyte–Based Assessment of Degree of Immunosuppression in Human Immunodeficiency Virus Infection (39)**

	NO IMMUNOSUPPRESSION		MODERATE IMMUNOSUPPRESSION		SEVERE IMMUNOSUPPRESSION	
AGE GROUP	CD4 CELL COUNT, /μL	CD4, %	CD4 CELL COUNT, /μL	CD4, %	CD4 CELL COUNT, /μL	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

TABLE 7. **Clinical Staging of HIV Infection (39)[a]**

HIV STAGE	DEFINITION
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

HIV=human immunodeficiency virus.
[a]Until 2014, CD4-based immunosuppression (none, moderate, severe) was categorized separately from a clinical staging in children (<13 years old): N, no signs or symptoms; A, mild signs or symptoms; B, moderate signs or symptoms; C, severe, AIDS-defining illness.(40)

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 and adherence to therapy. Patients generally achieve a undetectable viral load within 6 months, although 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 because continued nonadherence 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 toxic effects (Table 5). For patients having difficulty taking (eg, because of poor palatability) or tolerating (eg, because of 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 as well as robust adherence counseling and support.

Drug-drug interactions among different ARV drugs and between ARV and non-ARV drugs (including nonprescription and herbal medicines) are common, complicated, and potentially dangerous. Interactions can result in excessive toxic effects or loss of efficacy. As part of every clinical encounter, and especially when a 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. (45)(46)(47)

Prophylaxis and Immunizations for HIV-Infected Infants, Children, and Adolescents

Effective ART markedly reduces the risk of OIs and improves the protective response elicited by many immunizations.

TABLE 8. **Summary of Recommendations for Starting Antiretroviral Therapy (17)(38)**

AGE	CD4 CELL COUNT, /μL (%)	HIV CLINICAL ILLNESS SEVERITY	RECOMMENDATION
<12 months	Any	Any	Treat all
1 to <3 years	<1,000 (<25)	Moderate or Severe	Treat for CD4 or clinical criteria Otherwise consider treatment, especially if VL >100,000 copies/mL
3 to <5 years	<750 (<25)	Moderate or Severe	Treat for CD4 or clinical criteria Otherwise Consider treatment, especially if VL >100,000 copies/mL
≥5 years	<500	Moderate or Severe	Treat for CD4 or clinical criteria Otherwise consider treatment for children, especially if VL >100,000 copies/mL; treat all adolescents and adults
Pregnant women	Any	Any	Treat all

HIV=human immunodeficiency virus; VL=viral load.

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).

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, all patients who have not yet started ART, and patients in whom ART fails to result in virologic suppression (most commonly due to nonadherence).

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 with CD4 values in the severe immune suppression category. In addition, children who have had PCP prophylaxis should receive cotrimoxazole prophylaxis after PCP treatment, at least until they have sustained improvement of immunologic status on ART.

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

As part of every HIV monitoring visit, patients should be evaluated for indicated vaccines. Although this recommendation seems common sense, studies have found that HIV-infected children are at increased risk of not receiving recommended vaccines. (48)(49) The recommended immunization schedule for HIV-infected children and youth is mostly the same as that for HIV-uninfected peers and is presented in Figure 1 and Figure 2 of the OI guidelines. (23) There are, however, several important exceptions (Table 9).

Although 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 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 to 5 years later. Furthermore, older children (ages 6-18 years) who never received the 13-valent pneumococcal conjugate vaccine should receive one dose. Finally, children who are not fully vaccinated against *Haemophilus influenzae* type b by age 5 years should receive a single dose of *H influenzae* type b conjugate vaccine.

HIV-infected children have been found to be less likely to respond to some vaccines. Thus, they should receive a 2-dose primary series of meningococcal conjugate vaccine instead of a single dose. They should also have anti–hepatitis B surface antibody measured 1 to 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 is safe and immunogenic in HIV-infected children without severe immunosuppression, (50) but, until more data are available, injectable influenza vaccine rather than live-attenuated intranasal influenza vaccine is recommended for all HIV-infected children. Measles-mumps-rubella (MMR) and varicella vaccines are recommended for HIV-infected children who do not have evidence of severe immunosuppression. The MMR and varicella combination vaccine, however, should not be used because 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 United States 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. On the basis of evidence that high proportions of US youth with perinatal HIV infection lack immunity to MMR 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 before 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 MMR 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 because the oldest people with perinatal infection are just reaching their 30s.

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- to 18-year-olds who have not received it	Elevated risk of pneumococcal infections
PPSV23	Administer 2-dose series beginning at age 2 years	Elevated risk of pneumococcal infections
Hib	Administer one dose of 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; Repeat MMR immunization (once receiving effective ART) if MMR doses given before effective ART established	Potential for live vaccines to cause illness in immunocompromised host; Lower probability and less durability of MMR vaccine response before ART

*ART=antiretroviral therapy; HBsAb=hepatitis B surface antibody; HBV=hepatitis B virus; Hib=*Haemophilus influenzae *type b; HIV=human immunodeficiency virus; MCV=meningococcal conjugate vaccine; MMR=measles-mumps-rubella; MMR-V=measles-mumps-rubella-varicella; PCV13=13-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine.*

The pattern of OIs and other illnesses that were typical of untreated HIV infection (Table 1) is uncommon today, although these problems continue to occur in children with unrecognized HIV infection and in children (especially adolescents) who are not able to receive cART reliably. The spectrum of problems seen in children and youth receiving effective cART includes complications of chronic HIV infection itself and 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 10).

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.

TABLE 10. **Complications and Problems in Perinatally Infected Children and Youth Receiving Effective cART**

BODY SYSTEM	PROBLEM OR COMPLICATION	DESCRIPTION
Neurocognitive	Learning or cognitive impairment, attention disorders, behavioral problems and mental illness	Common, likely multifactorial
Neurologic	Peripheral neuropathy, static encephalopathy	Was more common with certain drugs (stavudine, didanosine) no longer commonly used; residual effects of encephalopathy and/or strokes that occurred before effective cart
Growth and 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 therapy discontinued;
	Lipohypertrophy	Excessive central fat deposition in abdomen, breasts, dorsocervical "buffalo hump"; may be related to HIV and/or to certain ARV drugs
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 pre-cART lymphocytic interstitial pneumonitis 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 or damage	Related to ARV, concomitant viral hepatitis
Bone	Low bone mineral density; bone fragility	Multifactorial including certain ARV drugs (tenofovir) and traditional (non-HIV) risk factors for poor bone health
Reproductive health	Anogenital HPV-related dysplasia or malignant tumor	Not clear how much this risk is attenuated by effective cART
Malignant tumor	Overall higher rate	
Hematologic	Anemia, 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 multiorgan involvement; implicated in peripheral neuropathy, cardiomyopathy, and neurotoxicity

ARV=antiretroviral; cART=combination antiretroviral therapy; HIV=human immunodeficiency virus; NRTI=nucleoside reverse transcriptase inhibitor. 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.(51)*

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 on 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. (52) 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.

NOTE: The content of this article is solely the responsibility of the author and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development or the National Institutes of Health (NIH). The author is a U.S. government employee who must comply with the NIH Public Access Policy, and the author or NIH will deposit, or have deposited, in the NIH PubMed Central archive, an electronic version of the final, peer-reviewed manuscript to be made publicly available no later than 12 months after the official date of publication.

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PIR Quiz

1. An infant boy was delivered at term to a human immunodeficiency virus (HIV)–positive woman who received no prenatal care. Assuming the infant did not develop an intrauterine infection, the GREATEST risk of postnatal transmission of HIV infection from the mother to this infant would be associated with
   A. Breastfeeding.
   B. Changing diapers.
   C. Co-sleeping.
   D. Kissing the infant.
   E. Preparing formula.
2. An infant boy was delivered at term to an HIV-positive woman who received no prenatal care. The MOST appropriate first test for acquired HIV infection in this infant would be
   A. Cord blood HIV RNA polymerase chain reaction.
   B. Oral enzyme-linked HIV antibody immunoassay.
   C. Serum enzyme-linked HIV antibody immunoassay.
   D. Whole blood HIV DNA polymerase chain reaction.
   E. Serum Western blot for HIV antibodies.
3. An infant boy was delivered at term to an HIV-positive woman who received no prenatal care. An appropriate test for HIV infection was performed within a few hours after the infant's birth. To ensure the best outcome for the infant, he should also
   A. Be breastfed.
   B. Be placed in foster care.
   C. Not initiate the hepatitis B vaccine series at birth.
   D. Immediately start antiretroviral prophylaxis.
   E. Receive his first dose of oral cotrimoxazole now.
4. Which of the children below MOST requires prompt testing for HIV?
   A. Fourteen-month-old boy with his third episode of acute otitis media.
   B. Nine-month-old girl whose weight gain parallels the third percentile.
   C. Nine-month-old girl with active tuberculosis.
   D. Six-month-old boy with his second bout of oral candidiasis.
   E. Six-year-old girl with her first episode of herpes zoster.
5. On the basis of no more than mild HIV-related symptoms, a CD4 cell count of 570/μL, and a plasma viral load of 120,000 copies, a 5-year-old boy qualifies for combination antiretroviral therapy. You and your infectious disease consultant elect to treat. As the boy's primary care physician you should also
   A. Initiate azithromycin prophylaxis for *Mycobacterium avium* complex.
   B. Initiate cotrimoxazole prophylaxis for pneumocystis infection.
   C. Make certain your patient does not receive any more live virus vaccines.
   D. Notify the boy's kindergarten teacher of his HIV status.
   E. Order 23-valent pneumococcal polysaccharide vaccine.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

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Parent Resources from the AAP at HealthyChildren.org

- English: http://www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/Where-We-Stand-Preventing-Prenatal-Transmission-of-HIV-.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/sexually-transmitted/paginas/where-we-stand-preventing-prenatal-transmission-of-hiv-.aspx
- English: http://www.healthychildren.org/English/health-issues/conditions/sexually-transmitted/Pages/HIV-Human-Immunodeficiency-Virus.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/sexually-transmitted/paginas/hiv-human-immunodeficiency-virus.aspx

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