TECHNICAL REPORT

Diagnosis of HIV-1 Infection in Children Younger Than 18 Months in the United States

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ABSTRACT

The objectives of this technical report are to describe methods of diagnosis of HIV-1 infection in children younger than 18 months in the United States and to review important issues that must be considered by clinicians who care for infants and young children born to HIV-1–infected women. Appropriate HIV-1 diagnostic testing for infants and children younger than 18 months differs from that for older children, adolescents, and adults because of passively transferred maternal HIV-1 antibodies, which may be detectable in the child’s bloodstream until 18 months of age. Therefore, routine serologic testing of these infants and young children is generally only informative before the age of 18 months if the test result is negative. Virologic assays, including HIV-1 DNA or RNA assays, represent the gold standard for diagnostic testing of infants and children younger than 18 months. With such testing, the diagnosis of HIV-1 infection (as well as the presumptive exclusion of HIV-1 infection) can be established within the first several weeks of life among nonbreastfed infants. Important factors that must be considered when selecting HIV-1 diagnostic assays for pediatric patients and when choosing the timing of such assays include the age of the child, potential timing of infection of the child, whether the infection status of the child’s mother is known or unknown, the antiretroviral exposure history of the mother and of the child, and characteristics of the virus. If the mother’s HIV-1 serostatus is unknown, rapid HIV-1 antibody testing of the newborn infant to identify HIV-1 exposure is essential so that antiretroviral prophylaxis can be initiated within the first 12 hours of life if test results are positive. For HIV-1–exposed infants (identified by positive maternal test results or positive antibody results for the infant shortly after birth), it has been recommended that diagnostic testing with HIV-1 DNA or RNA assays be performed within the first 14 days of life, at 1 to 2 months of age, and at 3 to 6 months of age. If any of these test results are positive, repeat testing is recommended to confirm the diagnosis of HIV-1 infection. A diagnosis of HIV-1 infection can be made on the basis of 2 positive HIV-1 DNA or RNA assay results. In nonbreastfeeding children younger than 18 months with no positive HIV-1 virologic test results, presumptive exclusion of HIV-1 infection can be based on 2 negative virologic test results (1 obtained at $\geq 2$ weeks and 1 obtained at $\geq 4$ weeks of age); 1 negative virologic test result obtained at $\geq 8$ weeks of age; or 1 negative HIV-1 antibody test result obtained at $\geq 6$ months of age. Alternatively, presumptive exclusion of HIV-1 infection can be based on 1 positive HIV-1 virologic test with at least 2 subsequent negative virologic test results (at least 1 of which is performed at $\geq 8$ weeks of age) or negative HIV-1 antibody test results (at least 1 of which is performed at $\geq 6$ months of age). Definitive exclusion of HIV-1 infection is based on 2 negative

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words
HIV-1, infants, children, diagnosis, United States

Abbreviations
MTCT—mother-to-child transmission
WHO—World Health Organization
ELISA—enzyme-linked immunosorbent assay
IFA—indirect immunofluorescence assay
FDA—Food and Drug Administration
Ig—immunoglobulin
PCR—polymerase chain reaction
NAAT—nucleic acid amplification test
PBMC—peripheral blood mononuclear cell
virologic test results, I obtained at ≥1 month of age and 1 obtained at ≥4 months of age, or 2 negative HIV-1 antibody test results from separate specimens obtained at ≥6 months of age. For both presumptive and definitive exclusion of infection, the child should have no other laboratory (eg, no positive virologic test results) or clinical (eg, no AIDS-defining conditions) evidence of HIV-1 infection. Many clinicians confirm the absence of HIV-1 infection with a negative HIV-1 antibody assay result at 12 to 18 months of age. For breastfeeding infants, a similar testing algorithm can be followed, with timing of testing starting from the date of complete cessation of breastfeeding instead of the date of birth.

INTRODUCTION

Most children acquire infection with HIV-1 through mother-to-child transmission (MTCT) of the virus. MTCT of HIV-1 can occur in utero, at the time of labor and delivery, and postnatally through breastfeeding. Before treatment or interventions to prevent transmission were available, the rate of MTCT of HIV-1 in the United States was approximately 25%. Major successes have been achieved in prevention of MTCT of HIV-1 in the United States; the MTCT rate has decreased to less than 2% with antiretroviral treatment of HIV-1–infected pregnant women and, for women who do not yet require treatment of their HIV-1 infection, with the use of the following efficacious interventions to prevent transmission: antiretroviral prophylaxis, cesarean section before labor and before rupture of membranes, and complete avoidance of breastfeeding. The estimated annual number of perinatal HIV-1 infections in the United States has decreased from a peak of 1650 infections in 1991 to an estimated 111 infections in 2005. Similarly, the estimated number of perinatally acquired cases of AIDS in the United States peaked in 1992 (945 cases) but subsequently decreased by 95% by 2004 (90 cases).

Despite the dramatic decrease in rate of MTCT of HIV-1 and in the number of pediatric HIV infections and AIDS cases in the United States, MTCT of HIV-1 has not been eradicated in the United States. The timely and accurate determination of the HIV-1 infection status for all children born to HIV-1–infected women is essential. Concomitant with improvements in prevention of MTCT of HIV-1 in the United States, significant advances have been made in the treatment options for HIV-1–infected infants and children. Thus, in contrast to the early years of the epidemic, when therapy for HIV-1 infection was nonexistent or very limited, the outlook today for pediatric patients with HIV-1 infection is much improved. HIV-1 infection now represents, with appropriate therapy, a chronic disease; early antiretroviral treatment allows prolonged symptom-free survival with preservation of immune system function. Exclusion of HIV-1 infection is also important for HIV-1–exposed but uninfected children so that opportunistic infection prophylaxis does not have to be instituted or can be discontinued and so that age-appropriate immunizations for HIV-1–uninfected children can be administered.

Appropriate HIV-1 diagnostic testing for infants and children younger than 18 months differs from that for older children, adolescents, and adults because of passively transferred maternal HIV-1 antibodies, which may be present in the child’s bloodstream until 18 months of age. As work progresses on eradication of pediatric HIV-1 infection, knowledge and understanding of the available diagnostic modalities for infants and young children, as well as factors that affect the choice and timing of implementation of such diagnostic methods, is essential for the timely provision of appropriate care for both HIV-1–infected and –uninfected infants and young children. The objectives of this technical report are to describe methods of diagnosis of HIV-1 infection in children younger than 18 months in the United States and to review important issues that must be considered by clinicians who care for infants and young children born to HIV-1–infected women. Obviously, the protection of the privacy of health information as required by state and federal laws, as well as the laws and regulations regarding consent for HIV-1 testing, are important issues, but they are outside the scope of this technical report.

METHODS OF DIAGNOSIS OF HIV-1 INFECTION

Both clinical and laboratory-based methods for the diagnosis of HIV-1 infection in children have been developed. Laboratory-based methods include both immunologic and virologic assays.

Clinical Diagnosis

Beginning in the late 1980s, the World Health Organization (WHO) developed clinical case definitions and clinical staging systems for HIV-1 infection. In addition, the WHO and the United Nations Children’s Fund developed the “integrated management of childhood illness” strategy to provide guidelines for the diagnosis and management of sick children at the primary care level. However, evaluations of clinical staging systems for the diagnosis of HIV-1 infection in children in sub-Saharan Africa, especially in young infants, have suggested limited sensitivity. The WHO has released revised case definitions of HIV-1 infection for surveillance purposes and a revised clinical staging classification of HIV-1–related disease in adults and children. Included in these guidelines are clinical criteria for the presumptive diagnosis of severe HIV-1 disease (among HIV-1–seropositive, HIV-1–exposed children younger than 18 months in situations in which virologic testing is not available) to allow for the early initiation of antiretroviral therapy.

Similarly, in the United States, guidelines for the clinical staging of HIV-1 disease were developed in the early years of the epidemic. Subsequently, new definitions...
of HIV-1 infection in children were published,30 including clinical diagnosis of HIV-1 infection (a child younger than 18 months who is born to an HIV-1–infected mother and who meets criteria for diagnosis of AIDS on the basis of the 1987 surveillance case definition27 is defined as being HIV-1 infected). A clinical classification system for children, originally intended for the classification of severity of HIV infection for surveillance purposes, comprises 4 clinical stages that range from asymptomatic infection to AIDS.30 However, dependence on clinical signs and symptoms for the diagnosis of HIV-1 infection has been largely superseded in the United States and similar settings because of the availability of laboratory-based methods for diagnosis of HIV-1 infection. With virologic assays, the determination of HIV-1 infection status can be accomplished within the first few weeks of life.

**Laboratory-Based Methods of Diagnosis**

Laboratory-based methods for the diagnosis of HIV-1 infection can be divided into 2 groups: immunologic and virologic. Immunologic assays detect the antibody response to HIV-1 or the extent to which the immune system has deteriorated as a consequence of HIV-1 infection. Virologic assays detect HIV-1 genetic material or components of the virus. All laboratory tests used for the diagnosis of HIV-1 infection must be confirmed (ie, the diagnosis of HIV-1 infection is never based on only a single test result).

**Immunologic Assays**

Immunologic assays, which detect the antibody response to HIV-1 and are used as screening tests, include enzyme immunoassays or enzyme-linked immunosorbent assays (ELISAs) as well as rapid serologic tests. A Western blot assay or an indirect immunofluorescence assay (IFA) is used to confirm reactive screening test results. These assays are currently available.

Assays that provide an assessment of immune system abnormalities include CD4+ and CD8+ T-lymphocyte absolute counts and percentages, the CD4+/CD8+ T-lymphocyte ratio, and other assays. Such assays are not currently used routinely to diagnose HIV-1 infection but have been and are being evaluated for such use.

**Detection of HIV-1 Antibodies**

Antibodies against HIV-1 are found in essentially all HIV-1–infected individuals. An important exception is HIV-1–uninfected children who are born to HIV-1–infected women; even in the absence of infection with HIV-1, these children may have detectable HIV-1 antibodies until 18 months of age. Situations in which HIV-1–infected individuals fail to produce a detectable antibody response against this virus are unusual but have been observed during the acute (“preantibody” or “window”) phase of infection (ie, during the first several weeks after infection) and during the very late stages of HIV-1 infection, when immune suppression is severe.31

**Enzyme-Linked Immunosorbent Assays**

In general, an HIV-1 ELISA involves adding a patient’s fluid sample to inert substrates that contain HIV-1 antigen.32 Usually, diluted serum or plasma is used, but assays that use urine and oral fluid are also available. For assays that have been approved by the US Food and Drug Administration (FDA), see www.fda.gov/cber/products/testkits.htm. Positive and negative controls for each ELISA are tested in parallel with patient specimens. If anti–HIV-1 antibody is present in the test sample (primary antibody), it will bind to the HIV-1 antigen on the plate. The plate is then washed, and an enzyme-labeled secondary antibody (“conjugate”) is added and will bind to human antibody. A chromogenic chemical substrate is applied, which is modified by the enzyme, resulting in a color change in an inert substrate (eg, microtiter well or physical strip/spot). In the case of a microtiter well-based assay, a spectrophotometer measures the resultant optical density. In this situation, a positive, or reactive, ELISA result occurs if the optical density of a patient sample microtiter well significantly exceeds the value calculated as the “cutoff” value. The microtiter optical density cutoff value is determined by using specific algorithms particular to each test kit method, but all kits use, to some degree, the optical density of the parallel negative controls as part of their calculations. As noted above, any ELISA with a reactive (positive) result should be repeated on the same blood sample, and if the result of the ELISA is repeatedly reactive, then the result is confirmed with a Western blot or IFA (see “Indirect Immunofluorescence Assays”). In general, a negative result with the ELISA requires no further confirmatory testing, although for persons suspected of being in the preantibody or window period of early HIV-1 infection, virologic assays (see “Virologic Assays”) could be performed or follow-up testing with ELISAs could be performed at a later date.

False-negative results can occur among individuals who are HIV-1–infected but have not yet begun to produce antibodies against HIV-1 (ie, within the first 6 weeks of infection, including those with clinical signs and symptoms of the acute retroviral syndrome)33 or among individuals in the late stages of HIV-1 infection with concomitant hypogammaglobulinemia. It is important to note that false-positive ELISA results can occur among individuals with immune stimulation (eg, among those with acute [non–HIV-1] viral infections or auto-immune disorders, among pregnant women, and among recipients of multiple transfusions).32 Finally, because of transplacental transfer of maternal immunoglobulin G (IgG) antibody, children born to HIV-1–infected women are seropositive (even if the child is not HIV-1–infected). Therefore, a positive ELISA result in a child younger than 18 months must be confirmed virologically (see “Virologic Assays”) before the child can be considered...
HIV-1–infected. (However, a positive ELISA result confirms that the child was exposed to HIV-1.) There are no reliable HIV-1–specific antibody assays to differentiate between maternal and autologous antibody in the child.

ELISAs are less expensive than virologic assays, and they can be readily used for testing large batches of samples. However, their use in batch testing means that, generally, there is a delay of up to 1 week in obtaining test results, depending on the laboratory system used, and such delays often preclude their use in settings such as labor-and-delivery units. This factor was one impetus for the development of the rapid antibody tests described in the next section.

Rapid Tests A number of rapid serologic tests for detection of IgG antibodies against HIV-1 are now available (for assays that have been approved by the FDA, see www.ida.gov/cber/products/testkits.htm). Such assays are based on 1 of 4 principles: particle agglutination, immunodot (dipstick), immunofiltration, or immune chromatography.32 For example, test kits that include HIV-1 antigens attached to a test strip allow detection of HIV-1 antibodies, if present in the test fluid sample (oral fluid, whole blood, serum, or plasma), through a rapid, visually interpreted color change. Rapid HIV-1 antibody tests are comparable to ELISAs in both sensitivity (99.3%–100%) and specificity (98.6%–100%).34 They require no special instrumentation outside of the test kit, and results can be available in as little as 20 to 30 minutes. Some of these kits are licensed for point-of-care testing so that clinics without extensive laboratory facilities (but that meet state and federal standards and have appropriately trained personnel) can perform the tests on-site and report the result to the patient immediately. As with routine ELISAs, confirmation of positive results is necessary, but confirmation of a negative result is not. Note that ELISAs cannot be used to “confirm” a rapid-test result, and all reactive rapid HIV-1 test results should be confirmed with either a Western blot or an IFA.35

Semiquantitative Antibody Assays Traditional HIV-1 antibody assays have been modified to produce a semiquantitative value. Semiquantitative HIV-1 antibody assays evaluate the quantity of antibody and not simply its presence or absence. Thus, HIV-1–uninfected infants and young children would have decreasing quantities of maternal antibody as more time elapses after birth. Conversely, HIV-1–infected children would lack evidence of such a decrease in the quantity of antibody (because although maternal antibodies against HIV-1 will decay over time, the child will begin to produce antibodies against HIV-1). Although such assays have been advocated for the diagnosis of HIV-1 infection in pediatric patients in resource-limited settings,36 they have not been incorporated into routine HIV-1 diagnostic algorithms for infants and young children in the United States (because the optimal performance characteristics of such assays generally do not become apparent until late infancy).

Western Blot Assays An immunoblot assay, such as a Western blot assay, typically is used to confirm a reactive ELISA or rapid serologic test result as being truly positive. The Western blot assay detects and visualizes the presence of antibodies against specific HIV-1 proteins (structural and enzymatic).33 HIV-1 proteins are separated according to their molecular weight by electrophoresis and transferred electrophoretically to a membrane. The subsequent steps are similar to those of the ELISAs. A patient’s fluid sample (usually diluted serum or plasma, but assays that use urine and oral fluid are also available; for assays approved by the FDA, see www.ida.gov/cber/products/testkits.htm) is added to the membrane and incubated. If the patient’s sample contains antibodies against any of the blotted HIV-1 proteins, these antibodies will bind to them in the areas where the respective proteins are located on the membrane. If antigen-antibody binding takes place, it can be visualized by an enzyme-labeled reaction that involves an anti-Ig (causing visible “bands” to appear on the membrane where the antibody bound the protein).

Different organizations have developed criteria for interpretation of HIV-1 Western blot assay results on the basis of the pattern of bands observed. HIV-1 proteins and their corresponding bands on the Western blot are designated as “p” (protein) or “gp” (glycoprotein), along with molecular weight in kilodaltons. There are 3 groups: envelope (env) glycoproteins (gp41, gp120, gp160), nuclear (gag) proteins (p18, p24/25, p55), and endonuclease-polymerase (pol) proteins (p31/p34, p40, p51/p52, p65/p68). According to the criteria of the Association of State and Territorial Public Health Laboratory Directors,37 a positive assay result is one that indicates the presence of antibodies to any 2 of the following proteins: p24, gp41, or gp120/gp160. An assay result that indicates no reactivity against any HIV-1 proteins is interpreted as being negative. An assay result that shows reactivity against 1 or more of the HIV-1 proteins but not those required for a positive assay result is interpreted as being indeterminate.

Western blot assays are only performed as confirmation of a repeatedly reactive screening result (ELISA or rapid antibody test). A negative Western blot assay result indicates that the positive ELISA or rapid-test result represents a false-positive result and that the patient does not have HIV-1 antibodies. A positive Western blot assay result confirms the presence of HIV-1 antibodies; thus, in individuals older than 18 months, it is diagnostic of HIV-1 infection. A positive HIV-1 antibody assay result followed by an indeterminate Western blot assay is compatible with (1) an HIV-1–infected child with early HIV-1 infection (before the full range of HIV-1 antibodies have developed), and follow-up HIV-1 diagnostic tests (virologic assays and/or Western blot assay results)
4 weeks later would be positive; (2) an HIV-1–uninfected child, with false-positive ELISA or rapid-test results originally and repeat ELISA/Western blot assays performed 4 weeks later that give the same results as originally obtained and with negative virologic assay results; or (3) an HIV-1–uninfected child with gradual loss of passively acquired maternal HIV-1 antibodies.

**Indirect Immunofluorescence Assays** The IFA can be used as a confirmatory test for HIV-1 infection. This assay is simple to perform and is less time consuming and less expensive than many Western blot assays. However, it does require an expensive fluorescence microscope and experienced laboratory personnel to read and interpret the results. The IFA is similar to the ELISA. A microscope slide that contains cells (usually human T lymphocytes) that have been infected with HIV-1 is used. There is a control that consists of uninfected cells. The infected and control cells are attached (fixed) onto the slide in specific areas (wells). Test serum is added to each well. The slides are then washed and dried. Anti-human IgG labeled with a fluorochrome (a substance that fluoresces when exposed to ultraviolet light) is added and will bind to HIV-1 antibodies if present in the sample. If the slide exhibits cytoplasmic fluorescence, it is considered to be a positive (reactive) result, which indicates that HIV-1 antibodies are present.

**Immune System Deterioration as a Consequence of HIV-1 Infection**

Flow cytometry for immunophenotyping of lymphocytes is widely available in the United States. This method permits the enumeration of T-cell lymphocytes into CD4+CD3+ T-helper cells and CD8+CD3+ T-suppressor cells. The hallmark of progression of HIV-1 infection is depletion of CD4+ T lymphocytes, the major cellular target of HIV-1 in humans. Differences in CD4+ T-lymphocyte counts between HIV-1–infected and –uninfected infants may be detectable soon after birth. However, HIV-1–infected infants may maintain normal CD4+ T-lymphocyte absolute counts and percentages throughout infancy. The CD4+ T-lymphocyte percentage was evaluated as a surrogate marker of HIV-1 infection in west Africa, but the sensitivity of this marker was only 87% to 88% at 3 to 6 months of age.

As CD4+ T-lymphocyte depletion progresses, the ratio of CD4+ to CD8+ T lymphocytes decreases. A study explored the possibility of using CD4+ T-lymphocyte counts, CD8+ T-lymphocyte counts, and the CD4+/CD8+ T-lymphocyte ratio to distinguish between HIV-1–infected and –uninfected infants. In this study, infants who had positive results of HIV-1 DNA PCR testing. Additional evaluations of the CD4+/CD8+ T-lymphocyte ratio as a diagnostic modality have been conducted. Thus, this method of diagnosis of HIV-1 infection remains investigational.

Other immunologic differences between HIV-1–infected and –uninfected children, which may serve as the basis for diagnostic testing in the future, have been investigated. HIV-1 infection in infants is associated with certain phenotypic markers of lymphocyte activation and differentiation. For example, HIV-1–uninfected infants have higher CD3+, CD4+, and naive CD4+ T-lymphocyte counts, whereas HIV-1–infected infants have higher total CD8+, CD8DR+, CD45RA-DR+, and CD28-DR+ T-lymphocyte counts. Also, total IgG, IgA, and IgM concentrations are significantly higher among HIV-1–infected children than among HIV-1–uninfected children, although individual HIV-1–infected children may have normal concentrations.

**Virologic Assays**

The life cycle of HIV-1 begins with attachment of viral particles to cells via CD4+ T-lymphocyte receptors and various coreceptors. After entry into the cell, the virus uncoats. A DNA copy of the RNA genome is produced by the viral-encoded reverse transcriptase. The DNA provirus can either integrate into the host cell genome or it can remain unintegrated in the cytoplasm. Replication of HIV-1 does not occur until the provirus is integrated into the host cell genome and the cell becomes activated either in vivo or in vitro. In vitro activation can occur through the use of various agents, including interleukin 2. Mature viral particles are produced from RNA copies of integrated proviral sequences. Ultimately, budding of mature virions occurs at the cell surface. Virologic tests for the diagnosis of HIV-1 infection encompass culturing of the virus, using nucleic acid amplification tests (NAATs [ie, tests that detect HIV-1 nucleic acids such as HIV-1 DNA or HIV-1 RNA]), and testing for components of the virus (eg, assays for a viral capsid protein [p24 antigen]). Advantages and disadvantages of each of these diagnostic modalities are shown in Table 1.

**HIV-1 Culture**

HIV-1 culture involves incubating peripheral blood mononuclear cells (PBMCs) from a patient with in vitro–activated PBMCs from an HIV-1–uninfected volunteer and culturing for up to 6 weeks. The culture medium contains interleukin 2, which maintains the target PBMCs in an activated state susceptible to viral infection and replication. Therefore, high levels of viral replication occur within the target PBMCs if infectious HIV-1 is present. Measurement of p24 antigen in the culture supernatant using ELISA allows assessment of the growth of HIV-1 in the PBMCs. The culture is classified as positive for HIV-1 if a significant amount of p24
antigen is detected (usually defined as ≥30 pg/mL) and demonstrates significantly increasing concentrations of p24 antigen over subsequent culture supernatant fluid collection time points. The use of viral culture for the diagnosis of HIV-1 infection in infants and young children has been studied extensively.47–52 Although previously considered the gold standard of HIV-1 diagnostic assays for infants and young children, the disadvantages of viral culture (ie, that it is labor intensive, time consuming, costly, and poses a biohazard risk) are now generally considered to outweigh its advantages. HIV-1 culture has limited availability, and its routine use in the clinical care of HIV-1–exposed infants and young children has been supplanted by HIV-1 NAATs.

HIV-1 NAATs
HIV-1 NAATs that detect viral RNA or proviral DNA are the most widely used assays for diagnosis of children younger than 18 months. Because viral nucleic acid may be present in very small quantities in test samples, NAATs are used to increase the amount of HIV-1 proviral DNA or HIV-1 RNA, or the amount of positive signal, in a test sample.

HIV-1 DNA Assays
Amplification of proviral DNA allows detection of cells that harbor quiescent provirus as well as cells with actively replicating virus. HIV-1 DNA PCR assays involve separating double-stranded DNA located in PBMCs from the test sample into 2 single strands by heating. 53,54 On cooling, the HIV-1 DNA strands reanneal with complementary nucleotide sequences of HIV-1–specific primers in the reagent mixture, which allows synthesis of new complementary DNA strands. After 1 heating and cooling cycle, the number of DNA strands that contain the HIV-1 proviral sequence that originated in the test sample has doubled, and through repetition of these steps numerous times, amplification of the HIV-1 proviral DNA from the test sample proceeds in a logarithmic manner. After a set number of amplification steps, HIV-1 proviral sequences are detected by hybridizing amplified DNA to a synthetic, enzyme-labeled HIV-1 DNA probe. A positive result is indicated by a color change in a chromogenic substrate. The sensitivity of HIV-1 DNA assays for the diagnosis of HIV-1 infection in infants and young children has been evaluated (Table 2) in several studies51,52,55–62 and meta-analyses, 63,64 with estimates as high as 90% to 100% by 1 month of age.51,56,59 Similarly high specificity has been observed by 1 month of age in nonbreastfed infants.51,55,56,59

HIV-1 RNA Assays
HIV-1 RNA assays detect plasma (cell-free) viral RNA by using different techniques. Methods of amplification of HIV-1 RNA include target (nucleic acid sequence-based amplification and reverse-transcriptase PCR) and signal (branched-chain DNA) amplification techniques. For HIV-1 RNA assays approved by the FDA, see www.fda.gov/cber/products/testkits.htm. In the nucleic acid sequence-based amplification assay, quantitation of HIV-1 RNA is achieved with internal calibrators, which are amplified along with the patient’s sample. As part of the branched-chain DNA assay, a light-emitting chemical reaction occurs, with the amount of light produced being proportional to the amount of RNA in the sample. In reverse-transcriptase PCR, reverse transcriptase is used to convert RNA into DNA; subsequently, amplification is performed by PCR.

### TABLE 1
Advantages and Disadvantages of Virological Diagnostic Assays for HIV-1 Infection

<table>
<thead>
<tr>
<th>Diagnostic Assay</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Culture</td>
<td>Previously considered the gold standard for diagnosis of HIV-1 infection in infants</td>
<td>Labor intensive, Requires special laboratory and equipment, 2–3 wk required for determination of a positive assay result, Expensive, Potential biohazard</td>
</tr>
<tr>
<td>DNA assays</td>
<td>Most experience to date for diagnosis of HIV-1 infection in infants and young children</td>
<td>Costly, Requires special equipment, experienced laboratories, trained personnel, False-positive results if laboratory contamination occurs, Not currently licensed for use in diagnosing HIV-1 infection</td>
</tr>
<tr>
<td>RNA assays</td>
<td>Widely available, Short turnaround time</td>
<td>Costly, Requires special equipment, experienced laboratories, trained personnel, Low copy numbers (eg, &lt;10,000 copies per mL) may represent false-positive results, Not currently licensed for use in diagnosing HIV-1 infection</td>
</tr>
<tr>
<td>p24 Antigen assays</td>
<td>More affordable and easier to perform than the other assays</td>
<td>Requires specific equipment, trained personnel</td>
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These assays are available as “standard” or “ultrasensitive” assays, and the lower limit of detection possible when using the ultrasensitive assays is in the range of 50 to 75 HIV-1 copies per mL of plasma.

Numerous studies of the use of HIV-1 RNA assays for the diagnosis of HIV-1 infection in pediatric populations have been conducted, with the reported sensitivity of testing (Table 3) for such assays ranging from 25% to 50% within the first few days of life to 100% by 6 to 12 weeks of age. HIV-1 RNA assays have been assessed to be at least as sensitive as, or more sensitive than, HIV-1 DNA assays among young infants. Similarly high specificity by 6 to 12 weeks of age (as compared with HIV-1 DNA assays or HIV-1 culture) has been observed among nonbreastfed infants.

HIV-1 RNA assays are now commonly used to diagnose HIV-1 infection in infants. HIV-1 RNA assays are often more readily available than HIV-1 DNA assays because of the common use of RNA assays in follow-up testing of patients during treatment for HIV-1 infection. When HIV-1 RNA quantitative assays are used for diagnosis of infants and young children, a plasma viral load of ≥10,000 copies per mL is generally required before...
the assay result is interpreted as being positive. Infants with untreated HIV-1 infection typically have extremely high viral loads (eg, >100 000 copies per mL), and many experts agree that HIV-1 RNA assay results of <10 000 copies per mL should not be interpreted as definitively positive when used for diagnosis of HIV-1 in infancy, and the assay should be repeated on a plasma sample obtained through a separate venipuncture or fingerstick procedure to confirm that such a low-level positive result is a true-positive result.

**p24 Antigen Assays**

The viral protein p24 exists either bound to anti-p24 antibody or unbound (free) in the bloodstream of HIV-1–infected individuals. Many studies of p24 antigen for diagnosis of HIV-1 infection have been conducted over the past several years, with the sensitivity of the assay increasing with increasingly effective techniques used to dissociate p24 antigen from anti-p24 antibody (immune complex–dissociated p24 antigen detection). In general, p24 antigen assays have been used much less frequently than HIV-1 DNA- or RNA-amplification techniques for diagnosis of HIV-1 infection because of the relatively poor sensitivity of p24 antigen assays and the absence of readily available commercial, FDA-approved reagents. It should be noted that the ultrasensitive p24 antigen assay performed on plasma samples for diagnostic purposes has a sensitivity of 97% to 100% within the first 6 months of life. However, this assay has not yet been widely recommended for identification or exclusion of HIV-1 infection in infants in the United States, but it may have a role in infant diagnosis in resource-limited settings.

**FACTORS THAT AFFECT CHOICE AND TIMING OF USE OF DIAGNOSTIC MODALITIES**

Several important factors must be considered when choosing HIV-1 diagnostic assays for pediatric patients and when to use them. Such factors include the age of the child, the potential timing of infection of the child, whether the infection status of the child’s mother is known or unknown, the antiretroviral exposure history of the mother and of the child, and characteristics of the virus.

**Age of the Child**

As alluded to previously, serologic testing for HIV-1 in infants and young children born to HIV-1–infected women must be interpreted with caution because of transplacental transfer of maternal HIV-1 antibody. Studies of the decay of maternally derived antibodies to HIV-1 indicate that most children serorevert (ie, lose maternal antibodies) by 12 months of age. However, the median time to loss of maternal antibody has varied in different studies, with numbers of subjects ranging from 40 to 520 (eg, 7 months, 11.6 months, and 13.3 months), and a small proportion of uninfected children remained HIV-1 antibody-positive at 15 months or 18 months. Therefore, loss of maternal antibody (seroreversion) as an HIV-1–exposed child

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**TABLE 3 Sensitivity and Specificity of HIV-1 RNA Assays**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age of Child</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>No. %</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Delamare et al (1997)</td>
<td>0 to 10 d</td>
<td>48 25</td>
<td>13–37</td>
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<tr>
<td></td>
<td>10 d to 3 mo</td>
<td>39 100</td>
<td>95–100</td>
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<tr>
<td></td>
<td>7 to 41 d</td>
<td>58 97</td>
<td>88–100</td>
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<tr>
<td></td>
<td>42 to 93 d</td>
<td>39 95</td>
<td>83–99</td>
</tr>
<tr>
<td>Cunningham et al (1999)</td>
<td>≤1 wk</td>
<td>2 50</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>1 to 3 wk</td>
<td>9 66.7</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>4 to 6 wk</td>
<td>26 96.2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>≥7 wk</td>
<td>95 100</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>132 96.2</td>
<td>—</td>
</tr>
<tr>
<td>Young et al (2000)</td>
<td>Birth</td>
<td>53 47</td>
<td>33–61</td>
</tr>
<tr>
<td></td>
<td>2 mo</td>
<td>47 100</td>
<td>92–100</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>35 100</td>
<td>90–100</td>
</tr>
<tr>
<td></td>
<td>6 wk</td>
<td>19 94.7</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>24 wk</td>
<td>7 85.7</td>
<td>—</td>
</tr>
<tr>
<td>Neisheim et al (2003)</td>
<td>0 to 7 d</td>
<td>14 29</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>8 to 28 d</td>
<td>19 79</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>29 to 60 d</td>
<td>34 91</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>61 to 120 d</td>
<td>26 96</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>120 to 180 d</td>
<td>28 97</td>
<td>—</td>
</tr>
</tbody>
</table>

— indicates that data were not available.
grows older is informative (because it indicates the absence of HIV-1 infection), but HIV-1 seropositivity in a child younger than 18 months is not diagnostic (because a positive antibody test result during the first 18 months of life could represent either persistent maternal antibody in an HIV-1–uninfected child or antibody newly produced by an HIV-1–infected child). Thus, serologic testing of a child younger than 18 months generally cannot be used to diagnose HIV-1 infection; therefore, virologic assays are required. (However, a positive antibody test result in the infant generally indicates maternal HIV-1 infection.)

Potential Timing of Infection of the Child

Infants who are presumed to have been infected with HIV-1 in utero may have detectable virus at birth, whereas infants presumed to have been infected around the time of delivery may not have detectable virus until days or weeks after birth. Thus, in nonbreastfeeding populations, an accurate diagnosis of HIV-1 infection among children of HIV-1–infected women can be made during the first few weeks of life with virologic assays. The sensitivity of testing depends on the timing of the test; sensitivity increases with increasing age of the infant. It has been recommended that diagnostic testing with HIV-1 DNA or RNA assays be performed within the first 14 days of life, at 1 to 2 months of age, and at 3 to 6 months of age. Furthermore, if any of these test results are positive, repeat testing is recommended to confirm the diagnosis of HIV-1 infection. A diagnosis of HIV-1 infection can be made on the basis of 2 separate positive HIV-1 DNA or RNA assay results. The Centers for Disease Control and Prevention recently revised its surveillance definition for defining lack of HIV-1 infection in an HIV-1–exposed infant. In nonbreastfeeding children younger than 18 months with no positive HIV-1 virologic test results, presumptive exclusion of HIV-1 infection can be based on 2 negative virologic test results (1 obtained at ≥2 weeks and 1 obtained at ≥4 weeks of age); 1 negative virologic test result obtained at ≥8 weeks of age; or 1 negative HIV-1 antibody test result obtained at ≥6 months of age. Alternatively, among children with 1 positive HIV-1 virologic test result, presumptive exclusion of HIV-1 infection can be based on at least 2 subsequent negative virologic test results (at least 1 of which is performed at ≥8 weeks of age). Finally, children can be considered presumptively uninfected with negative HIV-1 antibody test results (at least 1 of which is performed at ≥6 months of age). Definitive exclusion of HIV-1 infection is based on 2 negative virologic tests (1 obtained at ≥1 month of age and 1 obtained at ≥4 months of age) or 2 negative HIV-1 antibody tests from separate specimens obtained at ≥6 months of age. For both presumptive and definitive exclusion of infection, the child should have no other laboratory (eg, no positive virologic test results) or clinical (eg, no AIDS-defining conditions) evidence of HIV-1 infection. Many clinicians confirm the absence of HIV-1 infection with a negative HIV-1 antibody assay result at 12 to 18 months of age.

The diagnosis of HIV-1 infection among infants and young children with a history of breastfeeding is more difficult because of continuing exposure to the virus perinatally. The exclusion of HIV-1 infection among breastfeeding infants and young children cannot be definitively accomplished until after cessation of breastfeeding. There is no consensus on the best approach to testing for HIV-1 infection after breastfeeding has stopped. Some clinicians use an HIV-1 diagnostic testing algorithm similar to that suggested for nonbreastfed infants, with timing of testing based on the date of complete cessation of breastfeeding instead of the date of birth (ie, testing at the time breastfeeding has stopped, again 1–2 months after cessation, and again 3–6 months after cessation), with confirmation of the absence of HIV-1 infection by negative HIV-1 antibody assay results at 12 to 18 months of age; serologic testing should be performed at least 6 months after complete cessation.

Maternal HIV-1 Infection Status

The diagnostic approach to an infant or young child differs according to whether the mother’s HIV-1 infection status is known. Children of HIV-1–infected women have maternal antibodies to HIV-1 during the first months of life, and these children may remain HIV-1–seropositive until 18 months of age. Therefore, serologic testing (except if the test result is negative) is not informative in children younger than 18 months, but does reflect the serostatus of the mother. Virologic testing generally is required to determine the HIV-1 infection status of the child.

Women of unknown HIV-1 serostatus and their newborn infants can undergo rapid HIV-1 testing in the peripartum period to ascertain the HIV-1 infection status of the woman and the HIV-1–exposure status of the infant. It is recommended that rapid testing be available at all hospitals that serve pregnant women and that prompt testing using the rapid HIV-1 antibody assays be performed for pregnant women or infants of unknown HIV-1 serostatus.

Rapid HIV-1 antibody testing should be completed and results should be available quickly, because the effectiveness of postexposure prophylaxis administered to the infant (if the mother did not receive prophylaxis) is greatest if initiated within the first 12 hours of life. If the rapid-test result is positive during the intrapartum or immediate postpartum period, antiretroviral prophylaxis can be administered to the mother and/or infant. Subsequent to initiation of antiretroviral prophylaxis, confirmatory testing for HIV-1 infection can be performed. If the confirmatory test result is ultimately negative (suggesting that the initial rapid HIV-1 antibody test result was a false-positive), prophylaxis can then be discontinued. If the confirmatory test result is positive, HIV-1
infection in the mother and HIV-1 exposure in the child are confirmed. In this situation, antiretroviral prophylaxis is continued, and additional testing is indicated (as described previously).

Antiretroviral Exposure History of the Mother and Child

There are limited published data regarding what effect, if any, maternal and/or infant antiretroviral exposure has on the results of HIV-1 diagnostic testing with NAATs. HIV-1 DNA has remained detectable in PBMCs and lymphoid tissues of HIV-1–infected children despite years of exposure to antiretroviral agents and even when HIV-1 RNA assay results have been negative. In some studies, detection of virus with DNA PCR assays has been reported not to vary according to receipt of maternal or infant antiretroviral prophylaxis. However, a study by Prasitwattanaseree et al suggested that the age at which HIV-1 infection was detectable (by using a DNA PCR assay) among 98 HIV-1–infected infants depended on the duration of exposure to zidovudine by the mother and the infant. Detectable infection at birth was less frequent among children with a longer maternal duration of zidovudine receipt. Among mothers with a short duration of zidovudine receipt, infants who received a long duration of zidovudine were diagnosed later than those who received a short duration. To date, studies have suggested that maternal and infant receipt of perinatal transmission prophylaxis with zidovudine or nevirapine does not decrease the sensitivity of HIV-1 RNA PCR assays performed during the first 6 months of age. More research is needed to answer the question of whether the antiretroviral exposure history of the mother or the child affects the results of HIV-1 diagnostic testing with NAATs.

Characteristics of the Virus

HIV-1 viruses are classified into 3 groups: the main group (group M) accounts for at least 90% of HIV-1 infections around the world (Fig 1). The other groups are the outlier group (group O) and the non-M/non-O group (group N). Within group M, clusters of related viral strains are classified into subtypes (clades): subtypes A, B, C, D, E, F, G, K, and O. More than 50% of HIV-1 infections globally are caused by subtype C viruses, which predominates in sub-Saharan Africa and India. Subtypes A and B also account for large proportions of infections worldwide. Subtype B viruses predominate in North America and Europe. In addition to these subtypes, recombinant viruses (for example, BC recombinant viruses) exist. Group O infections seem to be localized to western and central Africa. Infections with group N virus are extremely rare.

An estimated 16.7% of infants in whom HIV-1 was diagnosed in New York State between 2001 and 2002...
had infections with non–subtype B strains. False-negative results on HIV-1 DNA assays in infants and young children infected with non–subtype B viruses have been reported. Therefore, it has been recommended that, for young children undergoing HIV-1 diagnostic testing who were born to HIV-1–infected mothers whose HIV-1 infection may have originated outside of Europe or the United States, a sample from the mother be tested with a virologic assay at the same time as a sample from the child. The child’s assay results can be interpreted only if the maternal test result is positive for HIV-1. Because maternal virus could exist as multiple, perhaps recombinant “quasi species,” only 1 of which is transmitted to the child, this approach may not identify all HIV-1–infected children with subtypes other than B. Assays for amplification of HIV-1 proviral DNA or RNA that are sensitive to group O viruses and/or to group M/non-B subtypes have been developed. Although HIV-1 DNA PCR assays optimized for non-B subtype HIV-1 have had limited availability in the United States, the availability has improved recently. Because HIV-1 RNA assays are, in general, more widely availability in formats optimized to identify non-B subtype HIV-1 infection, one of the commercially available RNA assays may be preferable to HIV-1 DNA PCR for identification of the child with non-B subtype HIV-1 infection.

In addition to HIV-1, another human retrovirus associated with AIDS is HIV type 2 (HIV-2). In terms of the more conserved gag and pol genes, the 2 viruses share approximately 60% overall nucleic acid sequence homology. Otherwise, the 2 viruses share 30% to 40% homology. Similar to HIV-1, there are different subtypes of HIV-2 (subtypes A, B, C, D, E, F, and G), although only HIV-2 subtypes A and B seem to be established significantly in human populations. Although HIV-1 is the major cause of AIDS in the United States and elsewhere in the world, HIV-2 is most prevalent in west Africa. Therefore, most HIV infections in the United States are HIV-1 infections, but HIV-2 infections can be encountered in pediatric practice in the United States (although MTCT of HIV-2 occurs less frequently than MTCT of HIV-1, largely because of the lower maternal viral loads with HIV-2 infection).

Whether a specific HIV-1 diagnostic assay is also able to detect HIV-2 infection becomes important in the evaluation of infants and young children who are born to women who may have acquired HIV infection in west Africa. Both virologic and serologic assays for the diagnosis of HIV-2 infection have been developed. For HIV-2 diagnostic assays (as well as combined HIV-1 and HIV-2 assays) approved by the FDA, see www.fda.gov/cber/products/testkits.htm.

**CONCLUSIONS**

Appropriate HIV-1 diagnostic testing for infants and children younger than 18 months differs from that for older children, adolescents, and adults because of passively transferred maternal HIV-1 antibodies, which may be detectable in the child’s bloodstream until 18 months of age. Therefore, routine serologic testing of these infants and young children is generally only informative before 18 months of age if the test result is negative. Virologic assays, especially HIV-1 NAATs, such as HIV-1 DNA PCR assays, represent the gold standard for diagnostic testing of infants and children younger than 18 months. With such testing, the diagnosis of HIV-1 infection (as well as the presumptive exclusion of HIV-1 infection) can be established within the first several weeks of life among nonbreastfed infants. Important factors that must be considered when selecting HIV-1 diagnostic assays for pediatric patients and when choosing the timing of such assays include the age of the child, the potential timing of infection of the child, whether the infection status of the child’s mother is known or unknown, the antiretroviral exposure history of the mother and the child, and characteristics of the virus.

In infants and young children of HIV-1–infected women, HIV-1 antibody testing of the child is not helpful around the time of birth (because the result will be reactive because of passively acquired maternal antibody). However, if the mother’s HIV-1 serostatus is unknown, rapid HIV-1 antibody testing of the mother or the newborn infant to identify HIV-1 exposure of the infant is essential so that antiretroviral prophylaxis can be initiated within the first 12 hours of life. For HIV-1–exposed infants (identified by positive maternal testing or by positive antibody testing of the infant shortly after birth), it has been recommended that diagnostic testing with HIV-1 DNA or RNA assays be performed within the first 14 days of life, at 1 to 2 months of age, and at 3 to 6 months of age. If any of these test results are positive, repeat testing is recommended to confirm the diagnosis of HIV-1 infection. A diagnosis of HIV-1 infection is made on the basis of 2 positive HIV-1 DNA or RNA assays. In nonbreastfeeding children younger than 18 months with no positive HIV-1 virologic test results, presumptive exclusion of HIV-1 infection can be based on 2 negative virologic test results (1 obtained at ≥2 weeks and 1 obtained at ≥4 weeks of age); 1 negative virologic test result obtained at ≥8 weeks of age; or 1 negative HIV-1 antibody test result obtained at ≥6 months of age. Alternatively, among children with at least 1 positive HIV-1 virologic test result, presumptive exclusion of HIV-1 infection can be based on at least 2 subsequent negative virologic test results (at least 1 of which is performed at ≥8 weeks of age). Finally, children can be considered presumptively uninfected with negative HIV-1 antibody test results (with at least 1 of the tests performed at ≥6 months of age). Definitive exclusion of HIV-1 infection is based on 2 negative virologic test results (1 obtained at ≥1 month of age and 1 obtained at ≥4 months of age) or 2 negative HIV-1
antibody test results from separate specimens obtained at ≥6 months of age. For both presumptive and definitive exclusion of infection, the child should have no other laboratory (eg, no positive virologic test results) or clinical (eg, no AIDS-defining conditions) evidence of HIV-1 infection. Many clinicians confirm the absence of HIV-1 infection with a negative HIV-1 antibody assay result at 12 to 18 months of age. For breastfeeding infants, a similar testing algorithm can be followed, with timing of testing based on the date of complete cessation of breastfeeding instead of the date of birth.

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