Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Diagnose of HIV Infection in Infants and Children

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HIV infection can be definitively diagnosed through use of virologic assays in most non-breastfed infants with HIV exposure by age 1 to 2 months and in virtually all infants with HIV infection by age 4 to 6 months. Antibody tests, including the newer antigen-antibody combination immunoassays (sometimes referred to as fourth- and fifth-generation tests), do not establish the presence of HIV infection in infants because of transplacental transfer of maternal antibodies to HIV; therefore, a virologic test must be used.\(^1\,^2\)

Positive virologic tests (i.e., nucleic acid tests [NAT]—a class of tests that includes HIV RNA and DNA polymerase chain reaction [PCR] assays, and related RNA qualitative or quantitative assays) indicate likely HIV infection. The first test result should be confirmed as soon as possible by a repeat virologic test on a second specimen.\(^3\)

Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with 1 obtained at age \(\geq 1\) month and 1 at age \(\geq 4\) months, or 2 negative HIV antibody tests from separate specimens obtained at age \(\geq 6\) months.\(^4\)

Additional virologic diagnostic testing at birth should be considered for infants at higher risk of perinatal HIV transmission and at 2 to 4 weeks after cessation of antiretroviral prophylaxis.\(^5\)

A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen.\(^6\)

Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV nucleic acid test.\(^7\)

Diagnostic testing in children with non-perinatal exposure only or children with perinatal exposure aged \(>24\) months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV nucleic acid test may be necessary to diagnose HIV infection.\(^8\)

Note: The National Clinical Consultation Center provides consultations on issues related to the management of perinatal HIV infection (1-888-448-8765; 24 hours a day, 7 days a week).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children\(^9\) with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children\(^9\) from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children\(^9\) with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children\(^9\) from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

\(^{†}\) Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

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second specimen, because false-positive results can occur with both RNA and DNA assays. For additional information on HIV and RNA assays and diagnosis of Group M non-subtype B and Group O HIV-1 infections and HIV-2 infections, see the Virologic Assays to Diagnose HIV Infection in Infants Younger Than 18 Months With Perinatal HIV-1 Exposure section and Other Issues section below.

Antigen/antibody combination immunoassays which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are not recommended for infant diagnosis. The sensitivity of the antigen component in the first months of life is less than that of an HIV NAT, and antibody tests should not be used for diagnosis in infants and children less than 18 months of age. Children with perinatal HIV exposure aged 18 to 24 months occasionally have residual maternal HIV antibodies; definitive confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on a NAT (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations). Diagnosis in children aged >24 months relies primarily on HIV antibody and antigen/antibody tests (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months).

Infants who are found to have positive HIV antibody tests but whose mothers’ HIV status is unknown (see Identification of Perinatal HIV Exposure) should be assumed to be exposed to HIV and undergo HIV diagnostic testing as described below.

For antiretroviral (ARV) management of HIV-exposed and HIV-infected newborns, see the Antiretroviral Management of Newborns with Perinatal HIV Exposure.

Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

Confirmation of HIV infection is based on two positive virologic tests from separate blood samples in infants and children younger than 18 months. Figure 1 summarizes the timing of recommended virologic diagnostic testing for infants at low risk of transmission (based on maternal antiretroviral therapy [ART] and viral suppression) with additional time points to be considered for infants at higher risk and those on combination ARV prophylaxis regimens.

Figure 1. Recommended Virologic Testing Schedules for Infants Exposed to HIV by Perinatal HIV Transmission Risk

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Birth</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>10 weeks</th>
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<thead>
<tr>
<th>Higher Risk</th>
<th>Birth</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>10 weeks</th>
<th>4 months</th>
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Low Risk: Infants born to mothers who received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence.

Higher Risk: Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (late second or third trimester), were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.

* For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of life).

NAT= nucleic acid test
HIV infection can be presumptively excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥14 days and one at age ≥4 weeks) or one negative virologic test (i.e., negative NAT [RNA or DNA]) at age ≥8 weeks, or one negative HIV antibody test at age ≥6 months.\(^1\)\(^7\)

**Definitive** exclusion of HIV infection in a non-breastfed infant is based on two or more negative virologic tests (i.e., negative NATs [RNA or DNA], one at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months.

For both presumptive and definitive exclusion of HIV infection, a child must have no other laboratory (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and not be breastfeeding. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody-negative status.

*Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is recommended for infants with indeterminate HIV infection status starting at age 4 to 6 weeks until they are determined to be HIV-uninfected or presumptively uninfected.\(^1\)\(^0\) Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children and Initial Postnatal Management of the Neonate Exposed to HIV section).

**Virologic Testing at Birth for Newborns at Higher Risk of Perinatal HIV Transmission**

Virologic testing at birth should be considered for newborns at higher risk of perinatal HIV transmission,\(^1\)\(^1\)\(^-\)\(^1\)\(^6\) such as infants born to mothers living with HIV who:

- Did not receive prenatal care
- Did not receive antepartum or intrapartum ARV drugs
- Received intrapartum ARV drugs only
  - Initiated ART late in pregnancy (late second or third trimester)
- Were diagnosed with acute HIV infection during pregnancy
- Had detectable HIV viral load close to the time of delivery
- Received combination ARV drugs and did not have sustained viral suppression

Testing infants exposed to HIV close to the time of birth identifies 20% to 58% of infants with HIV infection; however, in one study that specifically evaluated infants born to mothers who had not received ARV drugs during pregnancy and hence were at higher risk of *in utero* infection, birth testing identified 66.4% of infants with HIV infection.\(^1\)\(^7\) Prompt diagnosis of infant HIV infection is critical to allow for discontinuing ARV prophylaxis and instituting early ART (see When to Initiate Therapy). Blood samples from the umbilical cord should not be used for diagnostic evaluations because of the potential for contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection *in utero* from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection.\(^1\)\(^1\),\(^1\)\(^2\),\(^1\)\(^8\)

**Virologic Testing at Age 14 to 21 Days**

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,\(^7\) and early identification of infection would permit discontinuation of neonatal ARV prophylaxis and initiation of ART (see Infants Younger than Age 12 Months and Table 5 in When to Initiate Therapy).
Virologic Testing at Age 1 to 2 Months

Testing performed at age 1 to 2 months is intended to maximize the detection of infants with HIV infection.\textsuperscript{19,20} Two studies found that although the sensitivity during prophylaxis was not associated with the type of maternal or neonatal ARV prophylaxis, the sensitivity of diagnostic HIV testing during the period of infant ARV prophylaxis was lower compared to the sensitivity during the subsequent testing interval at 3 months of age. Overall, in both studies, 89% of infants with HIV infection were identified by 4 to 6 weeks of age. Of those infants who had negative testing in the first 7 days of life, repeat testing at 4 weeks to 6 weeks of age during the period of neonatal ARV prophylaxis identified 76% of infants with HIV infection in one study,\textsuperscript{19} and 68% of infants with HIV infection in the second study.\textsuperscript{17} In both studies, infants with negative testing in the first 7 days of life were diagnosed when the next diagnostic test was performed at 3 months of age.

For infants at \textbf{higher risk of perinatal HIV transmission}, the Panel suggests an additional virologic test 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of age) given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis, may reduce the sensitivity of testing during prophylaxis.\textsuperscript{7,17,19} In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt recognition of infected infants, with an additional test at 8 weeks of life (2 weeks after cessation of prophylaxis at 6 weeks of life) to capture additional cases. For infants at low risk of transmission, a single test obtained at 1 to 2 months of age may be timed to occur 2 to 4 weeks after cessation of ARV prophylaxis.

An infant with two negative virologic tests (one at age $\geq 14$ days and the other at age $\geq 4$ weeks) or one negative test at age $\geq 8$ weeks can be viewed as \textbf{presumptively} uninfected, assuming the child has not had a positive virologic test, CD4 immunosuppression, or clinical evidence of HIV infection.

Virologic Testing at Age 4 to 6 Months

Infants with HIV exposure who have had negative virologic assays at age 14 to 21 days and at age 1 to 2 months, have no clinical evidence of HIV infection, and are not breastfed should be retested at age 4 to 6 months for \textbf{definitive} exclusion of HIV infection.

Antibody Testing at Age 6 Months and Older

Two or more negative HIV antibody tests performed in non-breastfed infants at age $\geq 6$ months can also be used to \textbf{definitively} exclude HIV infection in children with no clinical or virologic laboratory-documented evidence of HIV infection.\textsuperscript{21,22}

Antibody Testing at Age 12 to 18 Months to Document Seroreversion

Some experts confirm the absence of HIV infection in infants and children with negative virologic tests (when there has not been prior confirmation of two negative antibody tests) by repeat serologic testing between 12 and 18 months of age to confirm that maternal HIV antibodies transferred \textit{in utero} have disappeared.\textsuperscript{1} In a recent study, the median age at seroreversion was 13.9 months.\textsuperscript{23} Although the majority of infants who are HIV-uninfected will serorevert by age 15 to 18 months, there are reports of late seroreversion after 18 months (see below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.\textsuperscript{23-26}

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion ($\leq$24 Months of Age)

Non-breastfed children with HIV exposure with no other HIV transmission risk and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies up to age 24 months (these children are called late seroreverters).\textsuperscript{23-26} In one study, 14% of children with HIV exposure who were uninfected seroreverted after age 18 months.\textsuperscript{23} These children may have positive immunoassay results but indeterminate supplemental antibody tests (using Western blot or IFA). In such cases, repeat antibody testing at a later time
would document seroreversion. Due to the possibility of residual HIV antibodies, virologic testing (i.e., with a NAT) is necessary to definitively exclude or confirm HIV infection in children with perinatal HIV exposure who have a positive HIV antibody (or antigen/antibody) test at age 18 to 24 months.

**Postnatal HIV Infection in Children with Perinatal HIV Exposure with Prior Negative Virologic Tests for Whom There Are Additional HIV Transmission Risks**

In contrast to late seroreverters, in rare situations postnatal HIV infections have been reported in children with HIV exposure who had prior negative HIV virologic tests. This occurs in children who become infected through an additional risk after completion of testing (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months). If an HIV antibody test is positive at age 18 to 24 months, repeated virologic testing will distinguish residual antibodies in late-seroreverting (uninfected) children from children with antibodies due to true infection.

**Suspicion of HIV-2 or Non-Subtype B HIV-1 Infections with False-Negative Virologic Test Results**

Children with non-subtype B HIV-1 infection and children with HIV-2 infection may have false-negative virologic tests but persistent positive immunoassay results and indeterminate HIV-1 Western blot results. The diagnostic approach in these situations is discussed below in the sections on Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and on Virologic Assays to Diagnose HIV-2 Infections.

**Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months**

**Breastfeeding**

Breastfeeding is a known route of postnatal HIV transmission. Typical scenarios in the United States include women who have not been adequately counseled about infant feeding, women who breastfeed despite being counseled not to (e.g., women from communities where breastfeeding is the norm and women who fear that not breastfeeding would be stigmatizing, including those where avoidance of breastfeeding raise suspicions about maternal HIV infection), and women who learn of their HIV diagnosis only after initiating breastfeeding (e.g., women who were HIV negative during pregnancy but who acquire HIV infection postnatally; breastfeeding during acute HIV infection is associated with an increased risk of perinatal HIV transmission). Breast milk from a donor with unrecognized HIV infection at the time of donation is an additional risk factor. Infants who are breastfed by women living with HIV should undergo immediate HIV diagnostic testing, and counseling to discontinue breastfeeding should be provided. Follow-up, age-appropriate testing should be performed at 4 to 6 weeks, 3 months, and 6 months after breastfeeding cessation if the initial tests are negative. Diagnostic testing may be influenced by factors that include the transplacental transfer of maternal antibody resulting in residual antibody in children aged up to 24 months (women who acquired HIV infection before delivery), as well as the possibility of performing the test during acute HIV infection; thus, a NAT would be the choice for initial testing. The receipt of postnatal ARV prophylaxis may delay the detection of HIV infection (see Antiretroviral Management of Newborns with Perinatal HIV Exposure).

**Premastication**

Receipt of solid food premasticated, prechewed, or prewarmed by a caregiver living with HIV has been documented to be associated with risk of HIV transmission. If this occurs in children with perinatal HIV exposure aged 24 months or younger with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing, as they may have residual maternal HIV antibodies (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations).
Additional Routes of HIV Transmission

Additional routes of HIV transmission in children include sexual abuse or receipt of contaminated blood products. In such cases, maternal HIV status may be negative. If the maternal HIV status is unknown, age-appropriate testing should be performed as described for children with perinatal HIV exposure.

Acquisition of HIV is possible through accidental needlestick injuries, sexual transmission, or injection drug use in older children. Medical procedures performed in settings with inadequate infection control practices may pose a potential risk; although tattooing or body piercing presents a potential risk of HIV transmission, no cases of HIV transmission from these activities have been documented.43

Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with non-perinatal HIV exposure only or children with perinatal HIV exposure aged >24 months relies primarily on HIV antibody and antigen/antibody tests.1,44 Food and Drug Administration (FDA)-approved diagnostic tests include:

• Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen (fourth and fifth generation tests [the fifth generation test differentiates between HIV-1 and HIV-2 antibodies as well as HIV-1 p24 antigen]): Recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection (p24 antigen from HIV-1 non-B, non-M and HIV-2 strains may not be detected).45

• HIV-1/2 immunoassays (third-generation antibody tests): Alternative for initial testing.

• HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies: Recommended for supplemental testing.

• HIV-1 NAT may be necessary as an additional test to diagnose acute HIV infection.

• HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests): Alternative for supplemental testing but will not detect acute HIV infection.

Diagnosis of HIV-2 in children with non-perinatal exposure or children with perinatal exposure aged >24 months relies on the Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories (APHL) 2014 laboratory testing guidelines, which recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies for supplemental testing. This is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test; more than 60% of individuals with HIV-2 infection are misclassified as having HIV-1 by the HIV-1 Western blot.1,46 All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department; additional HIV-2 DNA PCR testing can be arranged by their public health laboratory or the CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is not conclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis (this assay is not commercially available).47,48

Virologic Assays to Diagnose HIV Infection in Infants Younger than 18 Months with Perinatal HIV-1 Exposure

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in plasma. Their specificity has been shown to be 100% at birth and at 1, 3, and 6 months of age and is comparable to HIV DNA PCR.19 HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before being interpreted as documentation of HIV infection in an infant.49,50 Testing at birth will detect infants who were infected in utero and not those who become infected from exposure during or immediately prior to delivery (i.e., in the intrapartum period). Studies have shown that HIV RNA assays identify 25% to 58% of infants with HIV infection from birth through the first week of life, 89% at age 1 month, and 90% to 100% by age 2 to 3 months (similar to results of HIV DNA PCR for early diagnosis of HIV).3,7,19,51
HIV RNA undergoes reverse transcription to double-stranded DNA, which persists intracellularly within an infected cell. HIV DNA PCR assays detect intracellular DNA, and usually remain positive in individuals receiving ARV treatment. In contrast, HIV RNA assays are affected by maternal antenatal treatment or infant combination ARV prophylaxis. In one study, the sensitivity of HIV RNA assays were not associated with the type of maternal or infant ARV prophylaxis, but HIV RNA levels at 1 month were significantly lower in infants with HIV infection receiving multidrug prophylaxis (n = 9) compared to levels among infants receiving single-drug zidovudine prophylaxis (n = 47) (median HIV RNA 2.5 log copies/mL vs. 5.4 log copies/mL, respectively). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log copies/mL) by age 3 months in both groups after stopping prophylaxis. Further studies are necessary to evaluate the sensitivity and predictive value of HIV RNA assays during and after receipt of infant ARV prophylaxis.

An HIV quantitative RNA assay can be used as a supplemental test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. This viral load can also be used to determine HIV genotype and guide initial ARV treatment in an infected infant. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting non-subtype B HIV (see Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections).

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing. It is the only qualitative RNA test that is FDA-approved. HIV DNA PCR And Related Assays

HIV DNA PCR is a sensitive technique used to detect intracellular HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at ages 1, 3, and 6 months. Studies have shown that HIV DNA PCR assays identify 20% to 55% of infants with HIV infection from birth through the first week of life, with the same caveat as for RNA testing that testing at birth will detect infants infected in utero and not those infected during the intrapartum period, but the percentage increases to more than 90% by 2 to 4 weeks of age and to 100% at ages 3 months and 6 months.

Two studies provided data on diagnostic testing at different time points in infants with confirmed HIV infection including those who had negative testing at birth (i.e., infants considered to be infected during the intrapartum period). A randomized, international study of 1,684 infants evaluated the efficacy of three different regimens of neonatal prophylaxis containing 6 weeks of zidovudine either alone or with two or three other ARV drugs; none of their mothers had received prenatal ARV drugs. Infant testing was performed at birth, 10 to 14 days, 4 to 6 weeks, and 3 and 6 months (no testing was performed between 6 weeks and 3 months). Ninety-three (66.4%) of 140 infants with HIV infection were identified at birth, and by 4 to 6 weeks of age, 89% of the 140 infants were identified. Of the 47 infants with HIV infection who had negative DNA PCR tests at birth, 68% were identified during the period of neonatal ARV prophylaxis at 4 to 6 weeks; by 3 months, all 47 infants were identified. More recent data from Thailand showed that, in non-breastfed infants, receiving an ARV prophylaxis regimen of zidovudine/lamivudine/nevirapine for 6 weeks was associated with a delay in first HIV DNA detection. In this cohort, up to 20% of HIV-exposed infants had their first positive DNA PCR test after 2 months of age, prompting the authors to recommend infant testing at 4 months of age, having discontinued neonatal prophylaxis for at least 4 to 6 weeks.

Although the AMPLICOR® HIV-1 DNA test has been widely used for diagnosis of infants born to mothers with HIV-1 infection since it was introduced in 1992, it is no longer commercially available in the United States. The sensitivity and specificity of non-commercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the FDA-approved commercial test.

The COBAS AmpliPrep/COBAS TaqMan HIV-1 qualitative test which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots may be used for infant diagnosis but is not FDA-approved.
Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections

Although HIV-1 Group M subtype B is the predominant viral subtype found in the United States, multiple subtypes and recombinant forms are found in the United States with a widespread geographic distribution. In an evaluation of infants with perinatal HIV infection diagnosed in New York state in 2001 and 2002, 16.7% of infants were infected with a non-subtype B strain of HIV, compared with 4.4% of infants born in 1998 and 1999. Among a group of 40 children attending a pediatric HIV clinic in Rhode Island during 1991 through 2012, 14 (35%) were infected with non-B HIV-1 subtypes. All 14 children with non-B subtypes were either born outside the United States or their parents were of foreign origin.

In an analysis of 1,277 unique sequences collected in Rhode Island from 2004 to 2011, 8.3% were determined to be non-B subtypes (including recombinant forms). Twenty-two percent of non-B subtypes formed transmission clusters, including individuals with perinatally-acquired infection. In an analysis of 3,895 HIV-1 sequences collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms). Among individual states, the percentage of non-B subtypes ranged from 0% (in 12 states) to 28.6% in South Dakota, with seven states having greater than 10%. Evolving immigration patterns may be contributing to local and regional increases in HIV-1 subtype diversity. Non-subtype B viruses predominate in other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia. Group O HIV strains are seen in West-Central Africa. Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions. Geographical distribution of HIV groups is available at http://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp.

Currently available real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay have improved sensitivity for detection of non-subtype B HIV infection and the less common Group O strains, compared to older RNA assays that did not detect or appropriately amplify many non-B subtypes and Group O HIV (see HIV RNA Monitoring in Children: General Considerations in Clinical and Laboratory Monitoring).

Thus, a real-time PCR assay or qualitative RNA assay, rather than a DNA PCR assay, should be used for infant testing when evaluating an infant born to a mother whose HIV infection is linked to an area endemic for non-subtype B HIV or Group O strains, such as Africa or Southeast Asia. Another indication is when initial testing is negative using a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody tests obtained at age ≥6 months provide further evidence to definitively rule out HIV infection. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or the CDC may be able to assist in obtaining referrals for diagnostic testing.

Virologic Assays to Diagnose HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Cape Verde, Ivory Coast, Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and parts of India. It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions. HIV-1 and HIV-2 coinfections may also occur, but these are rare outside areas where HIV-2 is endemic. HIV-2 is rare in the United States. Although accurate diagnosis of HIV-2 can be problematic, it is clinically important because HIV-2 strains are resistant to several ARV drugs developed to suppress HIV-1.

Infant testing with HIV-2-specific DNA PCR tests should be performed at time points similar to those used for HIV-1 testing when evaluating an infant born to a mother with a known or suspected HIV-2 infection. A mother should be suspected of being infected with HIV-2 if her infection is linked to an area endemic for HIV-2 infection or if her HIV testing results are suggestive of HIV-2 infection (i.e., positive initial HIV 1/2 immunoassay test, repeatedly indeterminate results on HIV-1 Western blot, and HIV-1 RNA viral loads at or below the limit of detection; however, the current recommendation to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test as described below). HIV-2 DNA PCR testing can
be arranged by the HIV surveillance program of the state or local health department through their public health laboratory or the CDC, because this assay is not commercially available. \(^{47,48}\) Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2. \(^{76,85}\)

**References**


64. Bush S, Tebit DM. HIV-1 Group O Origin, Evolution, Pathogenesis, and Treatment: Unraveling the Complexity


