HIV Diagnostic Testing

This is a PDF version of the following document:
Section 1: Screening and Diagnosis
Topic 3: HIV Diagnostic Testing

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Background

HIV Testing and the Care Continuum

HIV diagnostic testing is the crucial first step in the HIV care continuum.[1] Establishing a diagnosis of HIV has important implications for both HIV treatment and prevention. Accumulating evidence shows that persons living with HIV who take antiretroviral therapy without interruption have better clinical outcomes and reduced transmission of HIV to others.[2,3,4,5,6] Further, the diagnosis of individuals with acute or early HIV infection is very important in preventing forward transmission of HIV—studies have found that persons with acute HIV infection are approximately 20 times more likely to transmit infection to their sexual partners than are those with chronic infection, and approximately 10% of all new sexually-acquired HIV infections in the United States are due to transmission during the acute phase.[7,8,9,10]

Approach to HIV Testing in the United States

In 2014, the Centers for Disease Control (CDC) and Association of Public Health Laboratories (APHL) released a new HIV diagnostic algorithm to allow for more accurate diagnosis of acute HIV-1, more diagnosis of HIV-2, fewer indeterminate results, and faster turnaround time for completion of the testing algorithm.[11] This HIV diagnostic algorithm is discussed in detail below in the section CDC Recommended HIV Testing Algorithm; the general HIV testing approach consists of initial screening with a fourth-generation antigen-antibody test, with follow-up testing of reactive samples using an HIV-1/2 differentiation assay (which can also provide antibody confirmation). Since none of the initial antibody or antigen-antibody screening tests are considered definitive for a diagnosis of HIV, confirmatory testing is always required. From a practical standpoint, the same patient blood sample can be used for initial screening test and the HIV differentiation assay. When using point of care sampling, such as an oral swab or fingerstick blood sample, the confirmatory testing requires obtaining an additional sample.

Clinical Laboratory Improvement Amendments (CLIA) Criteria

With a range of HIV diagnostic tests now available, the testing process can occur in a wide range of clinical and non-clinical settings. Most HIV testing is performed in a laboratory setting and the time required to perform the tests varies significantly, but some laboratory tests can be performed in less than an hour. Several point-of-care rapid tests are now available that can be performed in clinical or non-clinical settings. In the United States, the Centers for Medicare and Medicaid Services (CMS) regulates all clinical laboratory testing through the Clinical Laboratory Improvement Amendments (CLIA). As part of this process, CLIA has established a three-level test complexity criteria and this applies to the different HIV testing procedures:

- **Waived**: These tests are considered simple to perform, low-risk, and can be performed with
minimal training; specimens do not require centrifugation for testing.

- **Moderate Complexity**: Although these tests are considered simple to perform the testing involves using plasma or serum specimens, and program participation in an external proficiency testing program.

- **High Complexity**: These tests involve multiple-step protocols and require trained laboratory personnel to perform, participation in an external proficiency testing program, and frequent checks on quality control.
Timing of Positive Laboratory Markers following HIV Infection

Fiebig Staging System

Laboratory markers of HIV infection appear in a consistent sequence after the infection and delineate the period from initial exposure to established HIV infection. The Fiebig staging system, first published in 2003 defines 6 distinct stages of initial HIV infection, ranging from stage I (emergence of HIV RNA) to stage VI (full Western blot reactivity) (Figure 1).[12] Following HIV acquisition, HIV RNA is first detectable on standard laboratory tests approximately 10 days after infection. The next marker to appear is p24 antigen, which typically reaches detectable levels 4 to 10 days after the emergence of HIV RNA. Next, IgM antibodies are detectable about 3 to 5 days later, and are gradually replaced by IgG antibodies, which appear 2 to 6 weeks after initial HIV RNA detection.[13,14] Investigators have examined time to positivity of various HIV tests in relation to when the HIV Western blot turns positive.[14]

CDC/APHL Defined Phases for Laboratory Testing

The 2014 Centers for Disease Control and Association of Public Health Laboratories document outlines the sequence of when laboratory markers turn positive (Figure 2) and the document defines the following four, laboratory-based and clinically relevant phases of HIV infection:[11]

- **Eclipse Period**: The initial interval after HIV infection when no laboratory markers are consistently detectable.
- **Seroconversion Window Period**: The interval between HIV infection and the first detection of HIV antibodies; the seroconversion window varies depending on the different HIV antibody assay used.
- **Acute HIV Infection**: The interval between detectable HIV RNA and the detection of HIV antibodies.
- **Established HIV Infection**: Refers to the time after which a fully developed IgG response has developed sufficient to meet the interpretive criteria for a positive Western blot or IFA.

Atypical Laboratory Markers if HIV infection Occurs while on PrEP

The diagnostic accuracy and timing of early HIV infection in patients who acquire HIV while taking preexposure prophylaxis with tenofovir-DF-emtricitabine may result in atypical laboratory patterns, such as delayed seroconversion, indeterminate results on HIV differentiation assays, and low-level viremia in the setting of acute or early infection.[15]
Laboratory Tests Used for the Diagnosis of HIV

Enzyme Immunoassay (EIA) Tests

The HIV enzyme immunoassay (EIA) test for HIV diagnosis was first licensed in the United States in 1985.\[16\] This assay is designed to have very high sensitivity and in the past was widely used as the initial laboratory diagnosis test in the HIV testing algorithm; a positive EIA test always requires further confirmatory HIV testing with another HIV assay. The EIAs are based on color change or fluorescence, which is analyzed relative to a standard cut-off.\[16\] The HIV EIA tests have improved with each generation; compared to first- and second-generation EIA tests, third-generation tests can detect HIV infection earlier and can detect HIV-2; some also detect group O HIV-1 (Figure 3).

- **First-Generation EIA**: detects immunoglobulin G (IgG) antibodies using crude viral lysates
- **Second-Generation EIA**: detects IgG antibodies using recombinant (synthetic) antigens or proteins
- **Third-Generation**: detects IgG and immunoglobulin M (IgM) with the antigen-antibody sandwich technique

Fourth-Generation Antigen-Antibody Combination Assays

The fourth-generation “combination” antigen-antibody assays detect both HIV-1 p24 antigen and HIV antibodies and thus can diagnose HIV infection earlier than conventional HIV antibody tests (Figure 4).\[11,17\] All positive fourth-generation antigen-antibody tests require confirmatory testing. Five FDA-approved fourth-generation antigen-antibody tests are available for use in the United States, including four laboratory-based tests (ARCHITECT HIV 1/2 Ag/Ab Combo Assay, GS HIV Combo Ag/Ab EIA, Bio Rad Bioplex 2200 HIV Ag-Ab Assay, and the Siemens ADVIA Centaur HIV Ag/Ab Combo Assay) and one rapid test (Alere Determine HIV-1/HIV-2 Combo). None of these assays use HIV-2 core antigen (p26 antigen), but cross-reactivity to HIV-1 p24 antigen can occur with the presence of HIV-2 p26 antigen.

- **ARCHITECT HIV 1/2 Ag/Ab Combo Assay**: This assay can detect HIV-1 p24 antigen, antibodies to HIV-1 (groups O and M), and antibodies to HIV-2. This test does not distinguish antigen from antibody as the cause of a positive test, nor does it distinguish HIV-1 from HIV2. The ARCHITECT assay has been evaluated in several studies and has demonstrated detection rates over 99% for established HIV infection and detection rates from 61% to 83% for acute HIV (with specificity above 98% in both established and acute HIV infection).\[18,19\]
- **Bio-Rad GS HIV Comb Ag/Ab EIA**: This assay can detect HIV-1 p24 antigen, antibodies to HIV-1 (groups O and M), and antibodies to HIV-2. A positive test does not distinguish p24 antigen from antibodies to HIV and it does not distinguish HIV-1 from HIV2. In a performance evaluation, the GS combination assay was shown to be 100% sensitive in detecting established previously confirmed HIV infection and more than 85% sensitive in detecting acute HIV infection, with specificity above 99% in both groups.\[20\]
- **Bio Rad Bioplex 2200 HIV Ag-Ab Assay**: This assay detects HIV-1 p24 antigen, antibodies to HIV-1 (groups O and M), and antibodies to HIV-2. In addition, this assay differentiates between HIV-1 p24 antigen, antibodies to HIV-1 antibodies, and antibodies to HIV-2 and thus can help identify patients recently infected with HIV-1 (antibody negative and HIV-1 p24 antigen positive). Investigators prospectively tested the BioPlex 2200 HIV Ag-Ab EIA on 1,505 routine serum samples and the assay had a sensitivity of 100% and specificity of 99.5%.\[21\] Additional testing on samples known to be positive for HIV-1 or HIV-2 and the differentiation capability of the assay for HIV-1, HIV-2, both HIV-1 and HIV-2, or early HIV infection was 100%, 90.7%, 100%, and 90.9%, respectively.\[21\]
- **Advia Centaur HIV Ag/Ab Combo Assay**: This two-wash antigen-antibody sandwich immunoassay detects HIV-1 p24 antigen, antibodies to HIV-1 (group M), and antibodies to HIV-2. This assay does not differentiate between p24 antigen and HIV antibodies. The Advia
Centaur HIV Ag/Ab Combo Assay was evaluated in more than 7,000 samples and found to have a sensitivity of 98.4% and specificity of 99.7%.[22]

- **Alere Determine Rapid HIV-1/2 Ag/Ab Test**: The Alere Determine HIV-1/2 Ag/Ab assay is a point-of-care rapid test that can detect HIV-1 p24 antigen, antibodies to HIV-1 (group 0), and antibodies to HIV-2. This assay is currently the only FDA-approved rapid fourth-generation test. This assay can differentiate p24 antigen from HIV antibody, but it does not differentiate HIV-1 from HIV-2.[23] This assay has excellent sensitivity and specificity for persons with chronic HIV, but the sensitivity for acute or very recent HIV infection is less than with most of the fourth-generation laboratory-based immunoassays.[24,25]

### HIV Differentiation Assays

Although several tests can distinguish HIV-1 from HIV-2, only two—the Geenius HIV-1/2 Supplemental Assay and the Multispot HIV-1/HIV-2 Test—have been approved by the FDA for use as an HIV-1/HIV-2 differentiation assay for supplemental HIV testing. From a practical standpoint, there is only one FDA approved HIV-1/HIV-2 differentiation assay, since the manufacturers of the Multispot withdrew this product from the market in July 2016 and replaced it with the Geenius HIV-1/HIV-2 Supplemental Assay.[26] Differentiating HIV-1 and HIV-2 is important to avoid misclassification of infection; studies have shown that the HIV-1 Western blot was erroneously interpreted as positive for HIV-1 in 46% to 85% of specimens from persons infected with HIV-2.[11]

- **Geenius HIV-1/HIV-2 Supplemental Assay**: The Geenius HIV-1/HIV-2 Supplemental Assay is a single-use immunochromatographic test that functions both as an HIV confirmatory test and an HIV-1 and HIV-2 differentiation assay (Figure 5). This assay utilizes multiple recombinant or synthetic peptides to detect HIV-1 antibodies (p31, gp160, p24, and gp41) and HIV-2 antibodies (gp36 and gp140). The test cassette contains 7 test lines, including the 6 HIV peptides and one control. A positive HIV-1 result requires at least 2 envelope peptides (gp160 and gp41) or 1 envelope peptide plus either the p24 or the polymerase peptide p31; a positive HIV-2 diagnosis requires reactivity to both HIV-2 envelope peptides gp36 and gp140.[27] Investigators have shown the Geenius assay is a reliable HIV confirmatory assay and this test is recommended by the CDC as the differentiation assay to use in the HIV testing algorithm.[26,28,29,30,31]

- **Multispot HIV-1/HIV-2 Test**: The Multispot HIV-1/HIV-2 Rapid test is now primarily of historical significance since manufacturing for this HIV-1/HIV-2 differentiation assay was discontinued in July 2016. Prior to July 2016, the Multispot HIV-1/HIV-2 test had been widely used as the recommended and FDA-approved test for distinguishing between HIV-1 and HIV-2.[11,32,33] The Multispot is still being used by some laboratories that have not depleted their stock of kits ordered prior to July 2016. The test requires fresh or frozen human serum or plasma and it can be completed in about 15 minutes. The device has four test spots: (1) procedural control (anti-human IgG), (2) HIV-2 peptide (peptide representing the immunodominant epitope of HIV-2 envelope protein gp36), (3) recombinant HIV-1 (recombinant envelope protein gp41), and (4) HIV-1 peptide (peptide representing the immunodominant epitope of HIV-1 envelope protein gp41) (Figure 6). Test spots that are reactive turn a purple color; the interpretation of the test is based on which spots are reactive. The major drawback of this test is that interpretation of a positive spot is subjective and can vary depending on the operator performing the test.

### Western Blot

The Western blot is a method in which individual HIV-1 proteins are separated by gel electrophoresis and then react with specific proteins in a patient’s serum (Figure 7).[34] The HIV-1 Western blot detects human antibodies that react to HIV-1 proteins that originate from three HIV-1 gene regions: env (gp41, gp120/160), pol (p31, p51, p66), and gag (p15, p17, p24, p55) (Figure 8). The HIV Western blot is used as a confirmatory test and typically becomes positive after about 5 to 6 weeks following initial HIV infection; as more protein bands become detectable the Western blot typically
evolves from a pattern of negative to indeterminate to positive. The Centers for Disease Control and Prevention and the Association of State and Territorial Public Health Laboratory Directors jointly established criteria for interpretation of Western blot tests for HIV.[34]

- **Positive Western blot**: The presence of at least two of the following bands: p24, gp41, and gp120/160.
- **Negative Western blot**: The absence of any bands.
- **Indeterminate Western blot**: The presence of any bands, but not meeting positive criteria. Indeterminate results typically involve p18 (also referred to as p17), p24, or p55, or any combination of these three proteins. Possible causes of an indeterminate Western blot include early HIV infection, HIV-2 infection, pregnancy, or cross-reactivity with other antibodies, such as in patients who have recently received an influenza immunization or who have autoimmune disorders.

**Rapid Point-of-Care HIV Tests**

Rapid point-of-care HIV tests are enzyme immunoassay (EIA) kits that have self-contained testing reagents and materials and typically can yield a test result within 40 minutes.[16, 35, 36] There are seven FDA-approved rapid point-of-care tests that the CDC identifies as suitable for use in clinical and non-clinical settings; these tests are all CLIA-waived.[35] Most rapid HIV tests detect both HIV-1 and HIV-2. One rapid fourth-generation antigen-antibody test (Alere Determine HIV-1/HIV-2 Combo) also detects HIV-1 p24 antigen, in addition to HIV-1 and HIV-2 antibodies. Certain rapid tests are approved for use with whole blood or oral fluid while other test platforms require plasma or serum. Multiple reports have shown problems with false-negative and false-positive test results with the oral fluid point-of-care test rapid test. Rapid point-of-care tests (including the Alere fourth-generation test) are less sensitive than fourth-generation laboratory-based tests for the detection of HIV infection during early HIV infection (Figure 9).[37, 38, 39, 40] All positive rapid HIV test results are considered as presumptive positives and require further supplemental testing.[11] This typically requires obtaining a second specimen from the patient. The main situations where rapid testing is performed include (1) emergency room encounters where it is unlikely that patients will return for results of standard HIV tests, (2) at hospitals for women in labor who had no HIV testing performed during their pregnancy, (3) occupational blood exposure for HIV when immediate results may be needed to determine whether to offer postexposure prophylaxis to a health care worker, and (4) in other clinical settings where a low likelihood of follow-up for HIV test results is anticipated.[16, 41, 42]

**In-Home HIV Testing**

In-home testing typically refers to either performing the test in its entirety at home (OraQuick In-Home Oral HIV Test) or collecting the test specimen at home and mailing it in for testing (Home Access HIV-1 Test System). Both of these commercially available tests provide individuals with an option for anonymous testing. In-home testing or in home specimen collection may be preferable for some persons who are reluctant to undergo HIV testing in medical settings, and it can be used by new sexual partners for mutual testing prior to engaging in a sexual relationship.[43, 44] Studies have shown that at-home testing is feasible and acceptable to patients,[44, 45, 46, 47, 48] though several concerns persist including cost of the test, lack of appropriate counseling for a positive test result, and access to confirmatory testing for a positive result, and low sensitivity for detecting recent HIV acquisition.

- **OraQuick In-Home Oral HIV Test**: The OraQuick In-Home Oral HIV Test is the only FDA approved test for performing at home. The test involves collecting an oral sample with a test device at home, placing the test device in a test kit vial that contains a developer solution, and then waiting 20 minutes to read the test result (the test must be read within 40 minutes). The client must read and interpret the test result; the OraQuick In Home web site has printed and video "How-to" instructions. The in-home test costs approximately $40 and contains a full set of easy-to-follow instructions; in addition, the OraQuick web site has an on-
line video on how to perform the test, information on understanding the test results, and phone numbers for a confidential Support Center that can answer customer questions in English and Spanish 24 hours a day and 7 days a week. As with all other rapid tests, a positive home HIV test result is considered a preliminary positive HIV test result and confirmatory HIV testing is required.

- **Home Access HIV-1 Test System**: The Home Access HIV-1 Test System is an anonymous HIV testing system that utilizes home collection of a serum specimen. This Home access test involves multiple steps, including (1) calling a toll free number to register the Home Access test number anonymously and to receive pre-test counseling, (2) using a retractable safety lancet (provided in the kit) to self-collect a fingerstick blood sample at home, (3) shipping the sample in a prepaid shipping envelope to a manufacturer-designated accredited laboratory, and (4) calling a toll free number the next day and using the registration number to anonymously obtain test results and post-test counseling.

**HIV RNA Testing**

Qualitative HIV RNA nucleic acid testing (NAT) is used in three situations: (1) in the 2014 HIV diagnostic algorithm to evaluate for possible acute infection when a specimen has a reactive fourth-generation HIV antigen/antibody test but a nonreactive or indeterminate HIV-1/HIV-2 differentiation test), (2) when a high suspicion of acute HIV exists, regardless of the fourth-generation HIV antigen-antibody results, and (3) to confirm chronic HIV-1 infection. Currently, the Aptima HIV-1 RNA Qualitative Assay is the only nucleic acid test approved for HIV diagnostic purposes. Quantitative HIV RNA nucleic acid testing (NAT) is used routinely in clinical practice for monitoring the viral loads of patients who have already been diagnosed with HIV, and many commercially available tests are capable of detecting viremia as low as 20 copies/mL. Given the very low limit of detection of most HIV quantitative assays, many clinicians use quantitative HIV RNA tests (“viral load” tests) rather than qualitative tests for diagnostic purposes, since the quantitative tests are more widely available.[16,49] Despite the ability of HIV RNA tests to identify very early HIV infection, it is not used as a routine HIV screening test due to cost and technical complexity.[16] In addition, approximately 0.5% of individuals who have chronic HIV infection and are not receiving antiretroviral therapy will have undetectable HIV RNA levels; these individuals are often referred to as elite controllers and would be misclassified as negative if HIV RNA were used as the sole screening test.[50]
CDC Recommended HIV Testing Algorithm

The CDC HIV testing algorithm, which was finalized in 2014 and then updated in 2018, allows for more accurate diagnosis of acute HIV-1, more accurate diagnosis of HIV-2, fewer indeterminate results (due to a shorter window period), and faster turnaround time than previous approaches (Figure 10).[11,26,51] Because no single test is capable of detecting HIV immediately following infection, some patients with very early HIV infection will escape detection with this test algorithm.[52]

Initial Testing

The recommended initial HIV test should be performed with a laboratory-based fourth-generation combination immunoassay that detects antibodies to HIV-1 and HIV-2 and also HIV-1 p24 antigen. Most of the commercially available fourth-generation antigen-antibody tests detect HIV-1 p24 antigen, antibodies to HIV-1, and antibodies to HIV-2. A positive initial test with a fourth-generation antigen-antibody test requires confirmation and differentiation of HIV-1 and HIV-2 infection. A person with a negative initial fourth-generation antigen-antibody test result is considered not infected with HIV infection, as long as a very recent (2 to 3 weeks) exposure to HIV has not occurred. If no recent exposure to HIV has occurred, further HIV testing is not required for evaluation of current HIV status.

Differentiation Assay

If the initial screening fourth-generation antigen-antibody immunoassay is reactive, a second type of HIV test is needed to confirm the initial test and to differentiate whether the infection is caused by HIV-1, HIV-2, or both. For this purpose, the CDC algorithm recommends using an HIV-1/HIV-2 antibody differentiation assay. In the United States, only the Multispot HIV-1/HIV-2 Rapid Test and Geenius HIV 1/2 Supplemental Assay are FDA-approved for differentiating HIV-1 from HIV-2 infection.[26,28,53] Note that the Multispot is no longer manufactured. Samples that are reactive with the HIV fourth-generation combination immunoassay and the HIV differentiation assay are considered positive and should be classified as HIV-1, HIV-2, or HIV-1 and HIV-2.

- Specimens that are reactive on the initial combination antibody/antigen immunoassay but either indeterminate or nonreactive on the differentiation assay require further testing with an HIV-1 nucleic acid (NAT) to evaluate the possibility of acute HIV infection versus a false-positive antigen-antibody test. In this situation, if the NAT is positive for HIV-1, the person is likely to have acute HIV-1 infection.
- With the recent implementation of the Geenius HIV-1/HIV-2 Supplemental Assay, several test results now occur that did not occur with the previously used Multispot HIV-1/HIV-2 test as the HIV differentiation assay.
- In the case of a reactive (“preliminary positive”) result from a rapid test, the specimen should be submitted for testing according to the full 2014 algorithm, beginning with the combination antigen/antibody immunoassay.[11]

HIV Nucleic Acid Testing

If the initial fourth-generation antigen-antibody immunoassay is positive, but the HIV-1/HIV-2 differentiation assay is negative further testing with an HIV-1 nucleic acid test should be performed. If both the fourth-generation antigen-antibody immunoassay and the HIV-1/HIV-2 differentiation assay are positive, then quantitative HIV RNA testing (viral load) is indicated—HIV-1 quantitative, HIV-1 RNA, or quantitative HIV-2 depending on whether HIV-1 or HIV-2 is identified on the differentiation assay.

Interpretation of Test Results
If the fourth-generation HIV-1/HIV-2 Ag/Ab combination assay nonreactive, then the interpretation is no infection with HIV-1 or HIV-2, unless the patient has been infected within the past 30 days. If acute HIV is suspected, then perform an HIV-1 RNA test.

If the fourth-generation HIV-1/HIV-2 Ag/Ab combination assay is reactive and the HIV-1/HIV-2 differentiation assay result shows reactive for HIV-1 and nonreactive for HIV-2, then conclude the patient has HIV-1 infection.

If the fourth-generation HIV-1/HIV-2 Ag/Ab combination assay is reactive, HIV-1/HIV-2 differentiation assay result HIV-1 nonreactive / HIV-2 reactive, then conclude the patient has HIV-2 infection.

If the fourth-generation HIV-1/HIV-2 Ag/Ab combination assay is reactive and the HIV-1/HIV-2 differentiation assay shows HIV-1 indeterminate (or negative) in conjunction with a nonreactive HIV-2, then several possibilities exist. In this scenario, follow-up testing with HIV-1 NAT (nucleic acid test, also referred to as HIV-1 RNA or HIV-1 viral load) is indicated. If the HIV-1 NAT is positive, the patient has acute HIV-1 infection. If the HIV-1 NAT is negative, the most probable scenario is that the initial reactive immunoassay result was a false-positive result and the patient does not likely have HIV-1 or HIV-2 infection. Alternatively, in a patient with HIV-2 risk factors, these test results could theoretically indicate acute HIV-2 infection. Follow-up testing with HIV-2 NAT should be considered. Since HIV-2 RNA is not detected in at least half of individuals infected with HIV-2, making a definitive diagnosis may require testing of HIV-2 proviral DNA.

**CDC Recommended HIV Testing Approach Prior to 2014**

The CDC HIV diagnostic algorithm recommended by the CDC prior to 2014 consisted of an initial EIA test (optimized for sensitivity) followed by a supplemental (confirmatory) Western blot (optimized for specificity).[34] This algorithm has several shortcomings. First, the initial EIA test does not detect acute HIV infection until approximately 25 days after acquisition. Second, the traditional algorithm relied on Western blot for confirmation of HIV infection, but the Western blot has a turnaround time of several days and can produce false negative or indeterminate results, particularly during early HIV infection, all of which complicate management decisions. Third, this traditional HIV diagnostic testing algorithm does not adequately identify persons infected with HIV-2.
Performance of Diagnostic Tests

Characteristics of a Screening Tests

The principles that define a good screening test are not unique to HIV infection but apply to medical screening in general. An ideal screening test will accurately identify individuals with the clinical condition of interest, without mistakenly diagnosing individuals who do not have the condition. In addition, use of screening tests is most effective when limited to conditions for which there is available, effective treatment that can directly target the disease and improve prognosis and outcomes.[54]

Sensitivity and Specificity

In relation to HIV testing, sensitivity refers to the proportion of true positives (persons who are infected with HIV) that are correctly identified by a screening test (Figure 11).[55] In general, very high sensitivity is desired for initial HIV screening tests since the ideal goal of the screening test is to not miss detecting anyone who has HIV infection. Thus, if the test is 100% sensitive and the person tests negative, you can be confident the individual tested does not have the infection. All HIV antibody tests approved for use in the United States have a sensitivity greater than 98% in diagnosing persons with chronic HIV infection.[14] Specificity is the proportion of true negative persons who are not infected with HIV that are correctly identified as HIV-negative by a screening test (Figure 12).[56] If a test is 100% specific and the person tests positive, you can be confident they have the disease. In the United States, initial HIV antibody tests have greater than 99% specificity for chronic HIV infection, and the specificity increases to nearly 100% when the initial test is combined with a supplemental HIV test.[29]

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

In contrast to sensitivity and specificity, which refer to the diagnostic ability of a screening test, the predictive value of a test refers to the likelihood that the test will give the correct diagnosis.[55] Positive predictive value is the proportion of patients with a positive HIV result who are correctly diagnosed (i.e. who actually have HIV disease). Negative predictive value is the proportion of patients with negative HIV results who are correctly diagnosed (i.e. who are actually negative for HIV disease).[55] Because screening tests are neither 100% sensitive nor 100% specific, the predictive value of tests is also imperfect: it is possible for persons to receive an incorrect result from a diagnostic test: these results are termed false negative and false positive test results. It is important to understand that the prevalence of a disease in a community impacts the predictive value of a given test, and predictive values in one study or in one community do not apply to all other settings.[55]

False-Negative HIV Tests

A false-negative HIV test result refers to a negative HIV test result in a person who actually has HIV infection(Figure 13). A false-negative HIV antibody test result most often occurs when performing antibody testing in a person with acute HIV infection or from laboratory error. In addition, rare causes of false-negative results include (1) testing in persons who have defects in HIV-specific immunity and thus fail to generate certain antibodies,[57,58,59,60], (2) following receipt of potent antiretroviral therapy very early after HIV acquisition,[61,62] (3) in patients with hypogammaglobulinemia,[63] and (4) after administration of potent immunosuppressant medications.[64] In adults with chronic HIV infection, the loss of HIV antibody (seroreversion) is exceedingly rare.[65] A false-negative p24 antigen test can occur in the first several weeks after HIV acquisition (usually positive by day 17); in addition, many persons with untreated chronic HIV infection do not have persistently detectable p24 antigen levels, often due to p24 antigen complexing with p24 antibody. False negative HIV RNA tests can occur in the first week or two after...
HIV acquisition (typically positive by day 10) and in persons chronically infected with HIV who have inherently strong immunologic control of HIV and thus may have undetectable HIV RNA levels in the absence of antiretroviral therapy.

**False-Positive HIV Tests**

A false-positive HIV test result is defined as a positive HIV test result in a person who does not have HIV infection (Figure 14). A false-positive HIV test may occur due to polyclonal cross-reactivity, which is more common in the setting of pregnancy, recent inoculation with influenza vaccine, autoimmune disorders, receipt of an investigational HIV-1 vaccine, receipt of gamma globulin, prior blood transfusions, HTLV-1/2 infection, recent incident viral infection, collagen vascular diseases, and laboratory errors.[66] When trying to determine whether a patient’s HIV screening test result is accurate, the pretest probability—the likelihood before the test was performed that the patient has HIV infection—can help with interpretation; for example, a person who injects drugs and shares needles has a higher pretest probability of having HIV than an asymptomatic pregnant woman who tested negative in her two previous pregnancies and has had no change in sexual partners. Further, the likelihood of an accurate HIV test result correlates directly with the prevalence of HIV in the testing community: the proportion of false-positive tests is higher in populations with low HIV prevalence (even if the screening test is highly sensitive and specific), whereas the proportion of false-negative tests is lower.[55]
Delivering Test Results to Patients

Follow-Up for Test Results

In the past decade, the percentage of people newly identified with HIV infection who received their test results has risen substantially. Data from CDC-funded HIV testing sites show that in 2013, 91.3% to 97.0% of persons who underwent HIV testing received their HIV test results. Innovative methods of HIV testing and HIV test result delivery are helping increase these numbers. In particular, delivery of HIV test results by telephone has been found to be both effective and acceptable to patients, and in multiple studies was shown to increase the numbers of persons who received their test results. From 2004 to 2006, the CDC examined the feasibility of HIV testing in outreach and community settings, including in bathhouses, needle exchange programs, public parks, bars, and shelters; in these settings, 1.1% of persons had a positive confirmatory test and 75% of these newly HIV diagnosed persons received results of their confirmatory HIV testing. Although not captured by the CDC-funded testing site data, the availability of home testing has likely also increased the proportion of persons who undergo HIV testing and receive their results; persons with positive results require confirmatory testing.

Communicating Test Results: The CDC offers practical advice for providers who offer HIV testing in their practice settings. Providers should be prepared to deliver results to patients in a private area and in a direct, neutral tone. The person delivering the test results should be knowledgeable about HIV, since patients may have questions about HIV infection, transmission to partners, and disclosure. Importantly, patients who receive a positive HIV test result should be linked to HIV care prior to leaving the testing setting, and have a scheduled appointment with an HIV provider. For patients who test negative for HIV, the provider should be prepared to provide HIV prevention counseling to help the patient remain HIV negative, including discussion of and referral for preexposure prophylaxis (PrEP) when indicated.
Special Diagnostic Situations

Diagnosis of Acute HIV-1 Infection

The laboratory diagnosis of acute HIV-1 infection is most reliably made with a positive HIV RNA (or HIV-1 p24 antigen) with a concomitant negative (or indeterminate) HIV antibody assay (Figure 15).[73,74,75] Use of fourth-generation HIV antigen-antibody (as recommended in the 2014 HIV diagnostic algorithm) detects HIV at about 17 days after HIV infection, which is significantly sooner than with rapid HIV tests or home HIV testing platforms (Figure 16) [13,52,76]. Regardless of what immunoassay is used, initial laboratory testing will fail to detect some individuals with very recent HIV infection. Thus, for individuals in whom initial HIV testing is nonreactive but acute HIV infection is strongly suspected, HIV RNA testing should be performed. Increased awareness of acute retroviral syndrome by both patients and medical providers can help facilitate diagnosis in the early stages of infection. Among persons recently infected with HIV, it is estimated that at least half develop a non-specific syndrome characterized by fever, myalgias, lymphadenopathy, pharyngitis, fatigue, headache, and rash.[77,78,79] Because HIV RNA levels are typically very high in acute retroviral syndrome, an HIV RNA nucleic acid test is uniformly positive at this stage of infection.

Diagnosis of HIV Infection in HIV-Exposed Infants and Children

The 2014 CDC HIV diagnostic algorithm does not address the diagnosis of infants and children exposed to HIV.[11] To diagnose HIV infection among infants younger than 18 months of age, the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection recommend using a virologic assay (HIV nucleic acid testing, or NAT) that directly detects HIV RNA or HIV DNA (either quantitative or qualitative tests can be used). Virologic diagnostic testing should be considered at birth for infants considered high risk for acquiring HIV and all infants with perinatal HIV exposure should have virologic diagnostic testing at 14-21 days, 1-2 months (preferably 2-4 weeks after cessation of antiretroviral therapy), and at 4-6 months).[80] In the United States, the Aptima HIV-1 RNA Qualitative Assay is the only FDA approved qualitative test, and the previously used Amplicor HIV-DNA test is no longer commercially available.[80] Use of HIV p24 antigen testing is not recommended in this setting because of the lower sensitivity and specificity in the first months of life when compared with virologic tests such as HIV nucleic acid testing. Maternal and/or neonatal receipt of antiretroviral prophylaxis may decrease both HIV RNA and HIV DNA levels in the infant with HIV infection during the first 6 weeks of life and thus may compromise the sensitivity of HIV nucleic acid tests if performed during the postexposure prophylaxis period and likely for about 2 weeks after stopping prophylaxis.[80,81,82] Serologic tests are generally not useful in confirming a diagnosis of HIV in infants less than 18 months of age because maternal anti-HIV antibodies are passively transferred to the infant and persist for 12-18 months. In contrast, a negative HIV antibody test after month 12 can be used as an indicator to support the absence of HIV infection.

Diagnosis of HIV-2 Infection

The 2014 HIV diagnostic algorithm improves the detection of HIV-2 by using an HIV-1/HIV-2 differentiation assay as the second step of the algorithm, after the combination antigen/antibody test; the Western blot is eliminated from the testing sequence.[11] Confirmation of HIV-2 infection can be challenging since HIV-1 RNA assays do not reliably detect or quantitate HIV-2. More recently, quantitative HIV-2 RNA assays have become available through the University of Washington Department of Laboratory Medicine (HIV-2 DNA/RNA Qualitative and HIV-2 RNA Quantitation) and the New York State Department of Health (HIV-2 Nucleic Acid Testing).[83] It is important to note, however, that a significant percentage of individuals with HIV-2 infection can have HIV-2 RNA levels that are undetectable on these assays. Therefore, in certain epidemiological settings (i.e., in a patient with HIV-2 risk factors), a person with a positive screening HIV-1/HIV-2 antibody test and confirmed HIV-2 positive antibody on the differentiation assay should be considered HIV-2 positive even if plasma HIV-2 RNA is undetectable with an HIV-2 assay. In previous versions of the CDC HIV
testing algorithm, the diagnosis of HIV-2 was often missed or delayed due to improper classification as HIV-1.[84] This is because the enzyme immunoassay (EIA) tests detect both HIV-1 and HIV-2 but do not distinguish between them, and the traditional algorithm relied on the HIV-1 Western blot for confirmation of infection.[11,84,85] Infection with HIV-2 may cause a negative, indeterminate, or positive HIV-1 Western blot due to cross-reacting antibodies. In the setting of HIV-2 infection, a common HIV-1 Western blot pattern is indeterminate, with the presence of gag bands (p55, p24, or p17) and pol bands (p66, p51, or p31), but absence of env bands (gp160, gp120, or gp41), because HIV-1 and HIV-2 share little similarity in the env gene (Figure 17).[86]
Summary Points

- In 2014, the Centers for Disease Control and Prevention (CDC) and the American Public Health Laboratories (APHL) jointly published new HIV diagnostic testing guidelines.
- Compared to previous screening algorithms, the current algorithm is more likely to detect acute HIV-1 infection, more accurately diagnoses HIV-2 infection, allows for faster turnaround time, and leads to fewer indeterminate results.
- An ideal screening test is sensitive, specific, and limited to conditions for which there is available, effective treatment that can directly target the disease and improve prognosis and outcomes.
- False-negative HIV screening test results can occur during acute HIV infection and false positive HIV screening test results may occur due to lab errors, and rarely, cross-reactivity with other antibodies.
- Laboratory markers of HIV infection (HIV RNA, p24 antigen, anti-HIV IgM antibody, anti-HIV IgG antibody) appear in a consistent sequence and are the basis for all of the HIV diagnostic tests.
- The CDC HIV testing algorithm recommends initial testing with a fourth generation combination antigen/antibody test, followed (for samples that are positive on the antigen-antibody test) by an HIV-1/HIV-2 differentiation assay. Testing for HIV RNA should be done in cases where the initial test is reactive but the differentiation assay is either nonreactive or indeterminate.
- Testing for HIV RNA may identify very early HIV infection (HIV RNA tests may be positive up to a week sooner than the fourth-generation combination antigen/antibody immunoassay), but HIV RNA is not generally used for screening due to the cost and technical complexity of the test.
- Rapid HIV tests and home HIV tests are additional options to help facilitate HIV screening and detection. A positive result on a rapid or home test is considered to be a presumptive positive and requires further testing in accordance with the full 2014 HIV testing algorithm.
- Diagnosis of acute HIV infection, diagnosis of infants and children exposed to HIV infection, and diagnosis of HIV-2 may present diagnostic challenges requiring additional consultation.
Citations


[PubMed Abstract]

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[PubMed Abstract]

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[CDC]


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73. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Considerations for antiretroviral use in special patient populations: acute and recent (early) HIV infection. October 25, 2018. [AIDSinfo] -


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- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. October 17, 2017. [AIDSinfo]


• U.S. Department of Health and Human Services: U.S. Food and Drug Administration. OraQuick In-Home HIV Test. [FDA] -
### Figures

**Figure 1 (Image Series) - Fiebig Classification for Early HIV-1 Infection**

*Image 1A: Characteristics of Fiebig Stages*


<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
<th>HIV RNA</th>
<th>p24 Ag</th>
<th>*EIA</th>
<th>Western blot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eclipse</td>
<td>11 days</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>1</td>
<td>5.0 days</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>5.3 days</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>3.2 days</td>
<td>(+)</td>
<td>(+)</td>
<td>IgM Positive</td>
<td>Absence of HIV-specific bands</td>
</tr>
<tr>
<td>4</td>
<td>5.6 days</td>
<td>(+)</td>
<td>(+)</td>
<td>IgM Positive</td>
<td>#Indeterminate pattern</td>
</tr>
<tr>
<td>5</td>
<td>88.6 days</td>
<td>(+)</td>
<td>(+/-)</td>
<td>Positive</td>
<td>Reactive, but absence of p31 (pol)</td>
</tr>
<tr>
<td>6</td>
<td>Open-ended</td>
<td>(+)</td>
<td>(+/-)</td>
<td>Positive</td>
<td>Reactive, including p31 (pol)</td>
</tr>
</tbody>
</table>

* EIA = enzyme immunoassay  
# Indeterminate Western blot: presence of HIV-1 specific bands that fail to meet criteria established by US FDA for positive HIV (reactivity to two of the following three bands: p24, gp41, gp120/160)
Figure 1 (Image Series) - Fiebig Classification for Early HIV-1 Infection
Image 1B: Graphic Timeline of Fiebig Stages

Figure 2 Timing of Positivity for HIV Diagnostic Tests

Abbreviation: POC = point of care

Figure 3 First, Second, and Third-Generation HIV Antibody Tests

Illustration: David H. Spach, MD

<table>
<thead>
<tr>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses crude viral lysate</td>
<td>Uses recombinant HIV antigens or peptides</td>
<td>Uses “Sandwich” EIA</td>
</tr>
<tr>
<td>Detects IgG antibodies</td>
<td>Detects IgG antibodies</td>
<td>Detects IgM and IgG antibodies</td>
</tr>
</tbody>
</table>
The fourth generation HIV-antigen-antibody assays contain components that will detect HIV-1 p24 antigen, antibodies to HIV-1, and antibodies to HIV-2. The HIV-1 and HIV-2 recombinant proteins vary from assay to assay.

Illustration by David H. Spach, MD
Figure 4 (Image Series) - Principles for Fourth-Generation HIV Antigen-Antibody Assays
Image 4B: Patient Sample Reacting with Components in Assay

In this example, the patient sample contains HIV-1 p24 antigen and anti-HIV antibodies that bind to the HIV-1 p24 capture antibody and the HIV recombinant proteins.

Illustration: David H. Spach, MD
Figure 4 (Image Series) - Principles for Fourth-Generation HIV Antigen-Antibody Assays
Image 4C: Reactive Fourth-Generation Antigen-Antibody Test

The fourth-generation antigen-antibody assay will turn positive with the presence of one or more of the following: HIV-1 p24 antigen, antibodies to HIV-1, or antibodies to HIV-2. With most of these assays, the positive reaction is non-specific and thus does not differentiate HIV-1 p24 antigen, antibodies to HIV-1, or antibodies to HIV-2. In addition, the assay will not determine whether more than one of these components are present in a positive reaction.

Illustration: David H. Spach, MD
The Geenius HIV-1/HIV-2 Supplemental Assay is a single-use immunochromatographic test that utilizes multiple recombinant or synthetic peptides to detect HIV-1 antibodies (p31, gp160, p24, and gp41) and HIV-2 antibodies (gp36 and gp140). The test cassette as shown here contains seven test lines, including the six HIV peptides and one control.

Figure 6A: Components of Multispot

Source: Centers for Disease Control and Prevention.
Figure 6 (Image Series) - Multispot HIV-1/HIV-2 Rapid Test
Image 6B: Interpretation of Multispot

- Nonreactive
- HIV-1 Reactive
- HIV-2 Reactive
- HIV Reactive (undifferentiated)
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot

Image 7A: Components Used in the HIV-1 Western blot

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot
Image 7B: Separation of HIV-1 Antigens with Gel Electrophoresis

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot
Image 7C: Transfer of HIV-1 Antigens to Nitrocellulose Membrane

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot
Image 7D: HIV-1 Antigens on Nitrocellulose Membrane

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot
Image 7E: Generation of HIV-1 Western blot Test Strips

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot
Image 7F: Analysis of Patient Serum Sample on HIV-1 Western blot Test Strips

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot

Image 7G: HIV-1 Antibodies Bound to HIV-1 Antigens on Western blot Test Strip

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot

Image 7H: Addition of secondary Anti-human Antibody Linked to Enzyme Signal

Illustration: David H. Spach, MD
Figure 7 (Image Series) - Process for Performing HIV-1 Western blot
Image 7I: Explanation of Components on Western blot

Illustration: David H. Spach, MD
### Figure 8 HIV-1 Western blot

This graphic shows the relationship of the HIV-1 genes and products with the corresponding band on the HIV-1 Western blot.

<table>
<thead>
<tr>
<th>HIV-1 Gene and Product</th>
<th>Band on Western blot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>env</strong></td>
<td></td>
</tr>
<tr>
<td>Precursor Protein</td>
<td>gp160</td>
</tr>
<tr>
<td>External Glycoprotein</td>
<td>gp120</td>
</tr>
<tr>
<td>Transmembrane Protein</td>
<td>gp41</td>
</tr>
<tr>
<td><strong>pol</strong></td>
<td></td>
</tr>
<tr>
<td>Reverse Transcriptase</td>
<td>p66</td>
</tr>
<tr>
<td>Reverse Transcriptase</td>
<td>p51</td>
</tr>
<tr>
<td>Endonuclease</td>
<td>p31</td>
</tr>
<tr>
<td><strong>gag</strong></td>
<td></td>
</tr>
<tr>
<td>Gag Precursor</td>
<td>p55</td>
</tr>
<tr>
<td>Core</td>
<td>p24</td>
</tr>
<tr>
<td>Matrix</td>
<td>p17</td>
</tr>
<tr>
<td>Nucleocapsid Precursor</td>
<td>p15</td>
</tr>
</tbody>
</table>
**Figure 9 Point-of-Care Rapid HIV Tests that are CLIA Waived**

Source: Centers for Disease Control and Prevention.

<table>
<thead>
<tr>
<th>Point-of-Care Rapid HIV Tests (CLIA Waived)</th>
<th>Detects</th>
<th>Time to Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alere Determine HIV-1/2 Ag/Ab Combo Test</td>
<td>HIV-1 Ab</td>
<td>20 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV-1 p24 Ag</td>
<td></td>
</tr>
<tr>
<td>Chembio DPP HIV-1/2</td>
<td>HIV-1 Ab</td>
<td>Blood: 10-25 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td>Oral fluid: 40 minutes</td>
</tr>
<tr>
<td>Chembio SURE CHECK HIV 1/2 Assay</td>
<td>HIV-1 Ab</td>
<td>15 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td></td>
</tr>
<tr>
<td>Clearview HIV 1/2 STAT-PAK</td>
<td>HIV-1 Ab</td>
<td>15 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td></td>
</tr>
<tr>
<td>BioLytical INSTI HIV-1/HIV-2 Antibody Test</td>
<td>HIV-1 Ab</td>
<td>&lt;2 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td></td>
</tr>
<tr>
<td>OraQuick ADVANCE Rapid HIV-1/2 Antibody Test</td>
<td>HIV-1 Ab</td>
<td>20 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td></td>
</tr>
<tr>
<td>Uni-Gold Recombigen HIV-1/2</td>
<td>HIV-1 Ab</td>
<td>10 minutes</td>
</tr>
<tr>
<td></td>
<td>HIV-2 Ab</td>
<td></td>
</tr>
</tbody>
</table>
Figure 10 2014 CDC AHPL Recommended Laboratory Testing for the Diagnosis of HIV Infection

This graphic shows the HIV testing algorithm as recommended in 2014 by the Centers for Disease Control and Prevention and Association of Public Health Laboratories.

Figure 11 (Image Series) - Sensitivity of HIV Diagnostic Test (Image Series) - Figure 11 (Image Series) - Sensitivity of HIV Diagnostic Test
Image 11A: Example of Sensitivity of HIV Diagnostic Test

Persons Infected with HIV: n = 50

HIV Antibody Testing: 49/50 Positive

Sensitivity: 49/50 = 98%
Figure 11 (Image Series) - Sensitivity of HIV Diagnostic Test

Image 11B: Sensitivity: Mathematical Expression

\[
\text{Sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}
\]
Image 12A: Example of Specificity of HIV Diagnostic Test

Specificity: 48/50 = 96%
Figure 12 (Image Series) - Specificity of HIV Diagnostic Test
Image 12B: Specificity: Mathematical Expression

Specificity = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}
Figure 13 (Image Series) - False-Negative HIV Diagnostic Test (Image Series) - Figure 13 (Image Series) - False-Negative HIV Diagnostic Test
Image 13A: Test Results for HIV-infected persons
Figure 13 (Image Series) - False-Negative HIV Diagnostic Test
Image 13B: False-Negative Identified
Figure 14 (Image Series) - False-Positive HIV Diagnostic Test (Image Series) - Figure 14 (Image Series) - False-Positive HIV Diagnostic Test
Image 14A: Test Results for HIV negative persons
Figure 14 (Image Series) - False-Positive HIV Diagnostic Test
Image 14B: False-Positive Identified

Persons NOT infected with HIV

HIV Antibody Testing

False Positive
Figure 15 Laboratory Markers with Acute HIV Infection
Figure 16 Diagnostic Test Performance in Early HIV Infection

<table>
<thead>
<tr>
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<th>HIV-2</th>
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<td>gp105/125</td>
</tr>
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<td>Transmembrane Protein</td>
<td>gp41</td>
<td>gp36/41</td>
</tr>
<tr>
<td><strong>pol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse Transcriptase</td>
<td>p66</td>
<td>p68</td>
</tr>
<tr>
<td>Reverse Transcriptase</td>
<td>p51</td>
<td>p53</td>
</tr>
<tr>
<td>Endonuclease</td>
<td>p31</td>
<td>p31/34</td>
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<tr>
<td><strong>gag</strong></td>
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<td>Core</td>
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<td>Matrix</td>
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<td>Nucleocapsid Precursor</td>
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</table>