

Procedure Manual for HIV-1 Rapid Testing by Alere Determine™ HIV-1/2 Ag/Ab Combo

I. Introduction & Principle

The standard laboratory HIV testing algorithm used in the United States consists of screening with an enzyme immunoassay (EIA) and confirmation of repeatedly reactive EIAs using immunoblot, nucleic acid amplification (NAT), Western blot or IFA depending on specimen type submitted. Results are typically reported within 48 hours to 2 weeks.

The Alere Determine™ HIV-1/2 Ag/Ab Combo is a single-use immunochromatographic test for the detection of circulating, free HIV-1 p24 antigen and/or antibody to HIV-1 or HIV-2 in fingerstick whole blood. This test system is intended for use as a point-of-care test to aid in the diagnosis of infection with either HIV-1 or HIV-2. This test is suitable for use in multi-test algorithms designed for the statistical validation of rapid HIV test results. When multiple rapid HIV tests are available, this test should be used in appropriate multi-test algorithms.

This test is to be used under the following CLIA complexity designation:

Waived testing for whole blood fingerstick samples only.

(Venipuncture whole blood, serum, and plasma samples require a Moderate Complexity designation and, therefore, cannot be used in testing sites having only a waived designation. Any modification by the laboratory to the test system or to the FDA- approved test system instructions will result in the test system no longer meeting the requirements for waived testing.)

The test device is a laminated strip that consists of a Sample Pad containing monoclonal biotinylated anti-HIV-1 p24 antibody, a Conjugate Pad containing monoclonal anti-HIV-1 p24 antibody-colloidal selenium and HIV-1 and HIV-2 recombinant antigen-colloidal selenium, and a nitrocellulose membrane with an immobilized mixture of recombinant and synthetic peptide HIV-1 and HIV-2 antigens in the Lower Test Area, immobilized streptavidin in the Upper Test Area, and an immobilized mixture of anti-HIV-1 and HIV-2 antigens, and HIV-1 p24 recombinant antigen and anti-HIV-1 p24 monoclonal antibody in the Control Area. Capillary whole blood obtained by fingerstick is applied to the Sample Pad followed by Chase Buffer that migrates by capillary action through the Conjugate Pad and then through the nitrocellulose membrane.

If free HIV-1 p24 antigen is present in the specimen, it binds with the monoclonal biotinylated anti-HIV-1 p24 antibody from the Sample Pad and then with monoclonal anti-HIV-1 p24 antibody-colloidal selenium from the Conjugate Pad to form a complex. This complex migrates through the solid phase by capillary action until it is captured by immobilized streptavidin at the Upper Test Area (labeled "Ag") where it forms a single pink/red "Ag" line. If HIV-1 p24 antigen is not present in the specimen or is below the limit of detection of the test, no pink/red line is formed. NOTE: The monoclonal biotinylated anti-HIV-1 p24 antibody used in this assay does not cross-react with HIV-2 p26 antigen.

If antibodies to HIV-1 and/or HIV-2 are present in the specimen, the antibodies bind to recombinant gp41 (HIV-1) and gp36 (HIV-2) antigen-colloidal selenium conjugates from the Conjugate Pad. The complex migrates through the solid phase by capillary action until it is captured by immobilized HIV-1 and HIV-2 synthetic peptide antigens and recombinant gp41 antigen at the Lower Test Area (labeled "Ab") and forms a single pink/red "Ab" line. If antibodies to HIV-1 or HIV-2 are absent or are below the detection limits of the test, no pink/red Ab line is formed.

To ensure assay validity, a procedural "Control" line containing a mixture of anti-HIV-1 antibody, HIV-1/2 antigens, HIV-1 p24 recombinant antigen and anti-HIV-1 p24 monoclonal antibody is incorporated in the nitrocellulose membrane. For a test result to be valid there must be a visible pink/red Control line present. During the test procedure, the colloidal selenium conjugates released from the Conjugate Pad will be captured by the antibodies and antigens immobilized in the Control Area and form a pink/red Control line for samples that are either positive or negative. NOTE: A pink/red Control line may appear even when a test sample has not been applied to the test unit.

II. Specimen Collection:

- A. Fingertick whole blood.
 - 1. Don personal protection clothing, e.g., a disposable gown or apron and gloves.
 - 2. Clean the finger of the person being tested with an antiseptic wipe.
 - 3. Allow the finger to dry thoroughly or wipe dry with a sterile gauze pad, if necessary, after 2 minutes of exposure time to the antiseptic.
 - 4. Using a sterile lancet, puncture the skin just off the center of the selected middle or ring fingertip and wipe away the first drop with sterile gauze. Avoid squeezing the fingertip to accelerate bleeding as this may dilute the blood with excess tissue fluid.
 - 5. Collect the sample from the second drop by touching the disposable Capillary pipette (provided in the test kit) to the drop of blood until the pipette is filled to the fill line (50uL). Avoid air bubbles.
 - 6. Test immediately following the test performance instructions.
- B. Specimen rejection criteria.
 - 1. Only fingertick whole blood is acceptable for testing.
 - 2. Venous whole blood is not to be used for testing.
 - 3. Serum and plasma may only be tested in laboratories certified to run moderate complexity tests.

III. Materials:

- A. Materials provided.
 - 1. Each kit contains the components to perform 25 or 100 tests:
 - a) Alere Determine™ HIV-1/2 Ag/Ab Combo Cards contained in an aluminum pouch.
 - b) Desiccant Package
 - c) Disposable capillary tubes coated with EDTA
 - d) Disposable Workstation
 - e) Chase buffer
 - f) Package Insert
 - g) Quick reference guide
 - h) Subject Notification Notices
 - i) Customer letter
- B. Accessories required and commercially available.
 - 1. Fingertick sample collection kit
 - 2. Alere Determine™ HIV-1/2 Ag/Ab Combo Controls
Cat. # 7D2628
- C. Materials required but not provided.
 - 1. Clock, watch, or other timing device
 - 2. Disposable gloves
 - 3. Impermeable gown or apron
 - 4. Sterile gauze
 - 5. Antiseptic wipes
 - 6. Biohazard disposal container
 - 7. Sterile safety lancet
 - 8. 10% bleach, prepared fresh daily
 - 9. Adhesive bandage
- D. Warnings: For *in vitro* diagnostic use
 - 1. Read the package insert completely before using this assay. Follow the instructions carefully as not doing so may result in inaccurate test results.

2. Before performing testing, all testing personnel must read and become familiar with the Standard Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus and other Blood-Borne Pathogens in Health-Care settings (1).
 3. Use of the kit with specimens other than those specifically approved for use with this device may result in inaccurate test results.
 4. An individual infected with HIV-1 and/or HIV-2 who is receiving highly active antiretroviral therapy (HAART) may produce false negative results.
- E. Storage Conditions
1. Alere Determine™ HIV-1/2 Ag/Ab Combo Cards
 - a) Store the test devices in their original aluminum pouches between 2°C (36°F) and 30°C (86°F).
 - b) Store Chase Buffer in its original vial between 2°C (36°F) and 30°C (86°F).
 - c) Do not freeze.
 - d) Do not open the pouch until ready to test.
 - e) When stored as indicated, kit components are stable until expiration date marked on the cards.
 2. Controls
 - a) The Alere Determine™ HIV-1/2 Ag/Ab Combo Control kits must be stored in a refrigerator between 2°C (36°F) and 8°C (46°F).
 - b) Do not use beyond the expiration date established by the manufacturer.
 - c) Open the Control Vials only when performing a test.
 - d) Recap and store the Control Vials in their original container in the refrigerator between 2°C (36°F) and 8°C (46°F) after use.
 3. Initial and date all controls and reagents upon receipt into the laboratory.
 4. Initial and date all controls and reagents when opened and placed into use.
- F. Handling Precautions
1. If the dessicant packet is missing, DO NOT USE. Discard the test cards and use a new test device.
 2. Do not use any device if the pouches have been perforated.
 3. Each device is for single use only.
 4. Do not use the kit past the expiration date printed on the card. Always check the expiration date prior to testing.
 5. Do not mix reagents from different lot numbers of kits.
 6. Adequate lighting is required to read the test results.

IV. Safety:

- A. Handle blood specimens and materials containing blood as if capable of transmitting infectious agents.
- B. Do not drink, eat, or smoke in areas where specimens are being handled or testing is being performed. Avoid any contact with hands, eyes or mouth during specimen collection and testing.
- C. Wear a long sleeved lab coat, disposable gown, or scrubs and disposable gloves (latex or nitrile) while handling and testing blood specimens. Use a fresh pair of gloves for each client. Wash hands or use an alcohol-based hand sanitizer between clients.
- D. Dispose of all used lancets in a puncture proof biohazard sharps container immediately after use.
- E. Since only 50 µL of blood is used in the testing process, used test units may be discarded in either a biohazard waste container or a normal trash container. If blood cannot be expressed from the cotton ball or gauze upon compression used to collect the blood specimen, they may also be disposed in a normal trash container. However, if blood can be squeezed from cotton balls or gauze, they must also be discarded into a biohazard waste container.
- F. Wash hands thoroughly after performing each test or utilize an alcohol-based hand sanitizer.
- G. The recommended method of disposal of biohazard waste is autoclaving for a minimum of 1 hour at 121°C. Disposable materials may be incinerated. Liquid wastes may be mixed with appropriate chemical disinfectants.
- H. Wipe all spills thoroughly with a solution of 10% bleach or other appropriate disinfectant. Fresh 10% bleach solution should be made daily.
- I. **NOTE: Do not autoclave solutions that contain bleach.** For additional information on biosafety, refer to "Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and other Blood-borne Pathogens in Health-Care Settings".(2)

V. Quality Control

- A. Controls
 1. Run the controls as described in the test procedure and follow the instructions as described in the interpretation of test results.
 2. Alere Determine™ HIV-1/2 Ag/Ab Combo Controls are available separately for use with Alere Determine™ HIV-1/2 Ag/Ab Combo assay.
 3. The HIV controls are used to verify the operator's ability to properly perform the test and to interpret the results.
 4. External control material (Alere Determine™ HIV-1/2 Ag/Ab Combo Control Pack) stored at refrigerated temperatures needs to be brought to operating temperatures (18°to 30°C or 64° to 86°F) prior to testing.
- B. Expected results
 1. Built-In Control Features:
 - a) The control line serves as a built-in positive internal control and gives confirmation of sample addition and proper test performance.
 - b) A pink/red line will appear in the upper Control area if the test has been performed correctly and the device is working correctly.
 2. HIV-1 Positive antibody control: A faint pink/red line will appear in the Ab test area. A pink/red line should also be present in the Control area.
 3. HIV-2 Positive control: A faint pink/red line will appear in the Test area. A pink/red line should also be present in the upper Control area.
 4. HIV-1 p24 Antigen Control: A faint pink/red line will appear in the Ag Test area. A pink/red line should also be present in the upper Control area.
 5. Negative control: a NONREACTIVE test result will be produced. There should be no visible line in either the Ag or Ab Test areas. A pink/red line should be present in the Control area.

C. Frequency of Controls

1. For sites testing **more than 25 clients per day** (high-volume), controls are to be run **once each day of testing**. (A day is defined as a 24-hour period. For example, if testing is conducted from 8 p.m. until 2 a.m. that would be considered one day.)
2. When testing **at an off-site or a mobile location**, controls are to be run **once each day of testing**, regardless of the number of clients being tested. (A day is defined as a 24-hour period. For example, if testing is conducted from 8 p.m. until 2 a.m. that would be considered one day.)
3. **For all other sites**, including sites testing **fewer than 25 clients per day** (low-volume), controls can be run **once per week** when testing is performed.
4. **In addition**, controls must be run and perform as expected before any patients are tested in the following situations:
 - a) With each new lot of test devices prior to placing them in service. (A test kit lot is defined as the number printed on the outside of the foil package containing the test devices).
 - b) Each new operator before testing any clients for the first time.
 - c) With each new shipment of test kits received (even if it is the same lot number in current use).
 - d) If there is any change in the conditions of testing (e.g. new location, lighting, temperature, etc.).
 - e) If the temperature of the test storage area has fallen outside of 2° to 30°C (36° to 86°F).
 - f) If the temperature of the testing area has fallen outside of 18° to 30°C (64° to 86°F).
 - g) Whenever two consecutive invalid test results are obtained on the same client.

D. Quality Control Records

1. Quality Control (QC) information is to be recorded on the appropriate QC Log Sheet. The information required includes name of test, site performed, date, time and person performing the test, lot numbers of all reagents and controls, expiration dates of all reagents and controls, expected results and observed results of controls.
2. Temperatures for the kit storage area and the area where the test is performed are to be recorded each day.

E. External Proficiency testing:

1. Testing facilities must enroll in an external proficiency program. Acceptable programs include the MDCH-Bureau of Laboratories Proficiency Testing Program, College of American Pathologists Proficiency or American Proficiency Institute.
2. The laboratory director or technical consultant will review results. Acceptable performance is an overall score of 80% or greater.
3. If fewer than five samples were tested, acceptable performance is 100%.
4. Unacceptable performance requires that the director or technical consultant approve a written corrective action plan, including but not limited to re-training.
5. Sometimes a proficiency testing result is returned as "ungraded" by the provider. This usually means that not enough laboratories obtained the result that was expected, and it *may* indicate a problem other than the proficiency of the site. However, the testing site must still compare its result to the expected result, and the laboratory director must determine whether corrective action is appropriate.

F. Corrective Action:

1. If the controls fail to yield the expected results, **DO NOT** perform any patient testing until performance issues are resolved and expected results are obtained and recorded.
2. If the temperature of the test area and/or test reagent storage area is outside the acceptable, do not test. Contact your laboratory director/technical consultant and initiate corrective action.
3. Document the corrective action taken; see the Quality Assurance Manual and Corrective Action Guidelines.
4. All corrective action reports must be reviewed and signed by both the Site Coordinator and the Laboratory Director.

VI. Test Procedure:

All components for the Alere Determine™ HIV-1/2 Ag/Ab Combo assay are ready to use as supplied.

A. Kit Component Preparation:

1. Open the aluminum pouch containing the Alere Determine™ HIV-1/2 Ag/Ab Combo Cards.
2. Remove the desired numbers of test units from the 5 or 10-Test Unit Card by bending and tearing at the perforation.
NOTE: Removal of the test units should start from the right side of the Card to preserve the lot number which appears on the left side of the Card.
3. Return the unused test units to the aluminum pouch and close the pouch with the ziplock.
NOTE: Store the unused cards and test units only in the aluminum pouch containing the desiccant package. Carefully close the ziplock, so that the cards are not exposed to ambient humidity during storage.
4. Lay the Test Unit flat in the workstation and remove the protective foil cover from each Test Unit. The test should be initiated within 2 hours after removing the protective foil cover from each Test Unit. *NOTE: Use of the workstation is optional. If the workstation is not used, place the Test Unit on a flat surface.*

For whole blood (fingerstick) samples using the disposable Capillary Tube:

Clean the finger of the person being tested with an antiseptic wipe. Allow the finger to dry thoroughly or wipe dry with a sterile gauze pad. Using a sterile lancet capable of producing 50 µL of blood, puncture the skin just off the center of the finger pad and wipe away the first drop with sterile gauze. Avoid squeezing the fingertip to accelerate bleeding. Collect the second drop of blood by holding the capillary tube horizontally, and touch the tip of the capillary tube to the blood sample. *Note: Filling of the capillary is automatic – do NOT squeeze the bulb while sampling. Maintain this position until the flow of the sample has reached the fill line and stopped.*

1. Align the tip of the Capillary Tube containing the blood sample with the Sample Pad (marked by the arrow symbol) and gently squeeze the bulb. Avoid air bubbles. Wait until all the blood is transferred from the Capillary Tube to the Sample Pad.

Caution: Do not lift the Capillary Tube from the Sample Pad before all the blood has been transferred – a bubble may form which will prevent the complete transfer of sample.

If a sample won't expel, cover the small opening at the mark on the capillary with a gloved finger. Then squeeze the bulb until the sample is fully dispensed onto the Sample Pad.

2. Wait for one minute, then apply one drop of Chase Buffer to the Sample Pad.
3. Read the test result between 20 and 30 minutes after the addition of the Chase Buffer. Do not read Test Results after 30 minutes.

Note: Discard the used pipette tips, Capillary Tube, Test Units and any other test materials into a biohazard waste container.

VII. Interpretation of Test Results:

ANTIBODY REACTIVE (Two Lines - Control and Ab Line)

A pink/red Control line appears in the Control Area AND a pink/red Ab line appears in the Lower Test Area of the Test Unit. The intensity of the Ab and Control lines may vary. Any visible pink/red color in both the Control and Lower Test Areas, regardless of intensity, is considered REACTIVE. A Reactive Test Result means that HIV-1 and/or HIV-2 antibodies have been detected in the specimen. The Test Result is interpreted as PRELIMINARY POSITIVE for HIV-1 and/or HIV-2 antibodies.

ANTIGEN (HIV-1 p24) REACTIVE (Two Lines - Control and Ag Line)

A pink/red Control line appears in the Control Area AND a pink/red Ag line appears in the Upper Test Area of the Test Unit. The intensity of the Ag and Control lines may vary. Any visible pink/red color in both the Control and Upper Test Areas, regardless of intensity, is considered REACTIVE. A Reactive Test Result means that HIV-1 p24 antigen has been detected in the specimen. The test result is interpreted as PRELIMINARY POSITIVE for HIV-1 p24 antigen.

Note: A test result that is Reactive for HIV-1 p24 antigen in the absence of reactivity for HIV-1 or HIV-2 antibodies may indicate an acute HIV-1 infection in the test subject. In this case the acute HIV-1 infection is distinguished from an established HIV-1 infection in which antibodies to HIV-1 are present.

ANTIBODY REACTIVE AND ANTIGEN (HIV-1 p24) REACTIVE (Three Lines - Control, Ab and Ag Lines)

A pink/red Control line appears in the Control Area AND a pink/red Ab line appears in the Lower Test Area AND a pink/red Ag line appears in the Upper Test Area of the Test Unit. The intensity of the Ag, Ab and Control lines may vary. Any visible pink/red color in the Control Area, the Lower Test Area and the Upper Test Area, regardless of intensity, is considered REACTIVE. The Test Result is interpreted as PRELIMINARY POSITIVE for HIV-1 and/or HIV-2 antibodies and HIV-1 p24 antigen.

NONREACTIVE (One Line – Control Line)

A pink/red line appears in the Control Area of the Test Unit, and no pink/red Ab or Ag line appears in the Lower Test Area and the Upper Test Area of the Test Unit, respectively A NONREACTIVE Test Result means that HIV-1 or HIV-2 antibodies and HIV-1 p24 antigen were not detected in the specimen.

INVALID (No Control Line)

If there is no pink/red line in the Control Area of the Test Unit, even if a pink/red line appears in the Lower Test Area or the Upper Test Area of the Test Unit, the result is INVALID and the test should be repeated. If the problem persists, contact Alere™ Technical Support.

VIII. Limitation of Method:

- A. Alere Determine™ HIV-1/2 Ag/Ab Combo must ONLY be used with capillary (fingerstick) whole blood at CLIA Waived Complexity test sites.
- B. Alere Determine™ HIV-1/2 Ag/Ab Combo must be used in accordance with the instructions in the Package Insert to obtain accurate results.
- C. This assay does not detect or has not been validated to detect HIV-2 antigen.
- D. AIDS-related conditions are clinical syndromes and their diagnosis can only be established clinically.
- E. For a Reactive result, the intensity of the test line does not necessarily correlate with the titer of antigen or antibody in the sample.
- F. Reactive test results should be confirmed by additional testing using other tests.
- G. A Nonreactive result does not preclude the possibility of exposure to HIV or infection with HIV.
- H. A person who has participated in an HIV vaccine study may develop antibodies to the vaccine and may or may not be infected with HIV.
- I. This assay has not been evaluated for newborn screening, cord blood specimens, or individuals less than 12 years of age.

- J. Specimens from individuals infected with HIV-1 and/or HIV-2 who are receiving highly active antiretroviral therapy (HAART) may produce false negative test results.
- K. Specimens from individuals with Toxoplasma IgG, human anti-mouse antibodies, rheumatoid factor, elevated triglycerides, herpes simplex virus infection, and hospitalized and cancer patients may give false positive test results.
- L. Immunosuppressed or immunocompromised individuals infected with HIV-1 may not produce antibodies to the virus. Testing with any kit designed to detect antibodies may give negative results in this incidence and would not be a reliable test method for such patients.
- M. Reading Nonreactive test results earlier than 20 minutes or any test results later than 30 minutes may yield erroneous result.
- N. If Rapid HIV reactive results are not confirmed as positive (discordant results), it should not be assumed the patient is negative or that appropriate procedures for handling blood specimens and materials in contact with blood can be discontinued. Patients with discordant results should be counseled to return for the collection of a new blood specimen in xx weeks for repeat screening and confirmation tests.

IX. Referral for confirmatory testing:

- A. Whenever the rapid HIV-1/2 test result is reactive, the testing site must have established procedures for referral of either test specimens or persons being tested for confirmatory testing.
- B. If specimens are collected on site, the site must establish procedures describing how to collect, label, process, store and document specimen transfer; transport the confirmatory test specimens to the site(s) where they will be tested; and obtain the confirmatory results to give the client/patients.
- C. Indicate on the specimen requisition form that the specimen is from an individual who had a reactive rapid test result. Affix the MDCH bright orange adhesive "OQ-R" label to both the specimen tube and the laboratory requisition.
- D. Sites not able to collect confirmatory test specimens must have a procedure in place for referring persons to another site to obtain this testing.

X. Confirmatory Testing Protocols:

- A. All reactive (preliminary positive) rapid test results must be followed up with confirmation specimen.
- B. Confirmatory testing can be done on blood (plasma, serum or dried blood spots) or oral fluid specimens.
- C. The reference laboratory will perform enzyme immunoassay (EIA) screening tests on all rapid test reactive specimens. Depending on specimen received, the reference lab will follow established algorithms. Serum and plasma specimens found EIA repeatedly reactive will be followed with a Multispot test to differentiate between HIV-1 and HIV-2 antibodies. Dried blood spot and oral fluid specimens found EIA repeatedly reactive will be followed with a Western blot test.

XI. Follow up testing when confirmatory testing is negative (discordant result):

- A. A reactive (preliminary positive) rapid test and a negative or indeterminate confirmatory test is considered a discordant result. Always follow the MDCH guidelines and procedures for recommending retesting and reporting of discordant results.
- B. The client should be re-tested as soon as possible to rule out pre-analytical (e.g. mislabeling), analytical (e.g., problem with kit), or post-analytical (e.g., wrong result reported on client) errors. The client should have a new blood specimen collected, and screening and confirmatory testing should be repeated.
- C. If the results are still discordant and the possibility of error and/or technical problems has been ruled out, collect a new blood specimen in four weeks and repeat screening and confirmatory tests.

XIII. References:

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