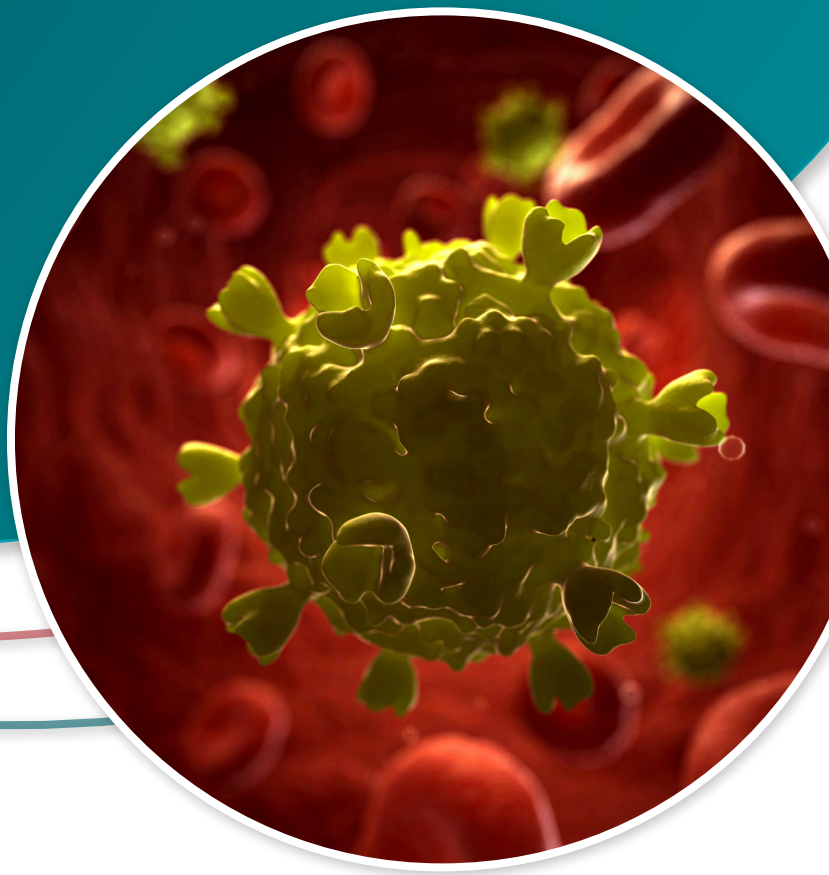
Suggested Reporting Language for the

HIV Laboratory Diagnostic Testing Algorithm

Fourth Edition, 2025



APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES®

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Introduction

To maximize public health impact, accurate and timely diagnostic HIV testing should be combined with clear result reporting and expedited linkage to medical care and services for infected persons. Laboratory reports should state each test that was performed, the result of each test, and the laboratory algorithm interpretation for the specimen.

The *Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm* was originally developed by the Association of Public Health Laboratory's (APHL's) HIV/Hepatitis Subcommittee to provide guidance to laboratories performing the 2014 HIV Laboratory Testing Algorithm.[1] This document and accompanying appendices are intended to clarify complex testing outcomes and guide laboratory reporting of test results to providers and health department surveillance programs. Information about the algorithm and definitions used throughout this document are addressed in the **Appendix (page 19)**. The suggested reporting language presented may require adjustments to meet individual facility or jurisdiction requirements; however, major deviations should be considered carefully because misinterpretation of HIV test results may have serious implications. Information presented in this document is not intended for use in patients who are receiving pre-exposure prophylaxis (PrEP).

Rationale for Document Update

This document is updated periodically as new information becomes available and/or changes related to the availability of US Food and Drug Administration (FDA)-approved HIV diagnostic tests occur. This 2025 Fourth Edition to *Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm* supersedes the previous versions[2, 3, 4] and has been prepared in response to the following developments:

- FDA approved the VioOne™ HIV Profile™ Supplemental Assay for confirmation of HIV-1 and HIV-2 antibodies in October of 2020.
- FDA approved three nucleic acid tests (NAAT) for diagnostic use: the cobas® HIV-1/HIV-2 Qualitative test (approved August 2020), the Aptima® HIV-1 Quant Dx assay (approved November 2020) and the Alinity m HIV-1 Assay (approved July 2022).
- The US Centers for Disease Control and Prevention (CDC) released *Technical Update for HIV Nucleic Acid Tests Approved for Diagnostic Purposes* (last reviewed May 2023).[5]
- CDC released an update to the clinical practice guidelines, *Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2021 Update*.[6]

Importance of Standardized Reporting Language

The use of standardized language when reporting laboratory results is particularly important for testing that involves multi-test algorithms. The HIV Laboratory Testing Algorithm[1, 7] (See **Appendix, page 19**) involves a series of tests, often performed by more than one laboratory, to determine the presence or absence of HIV infection.

Several available HIV diagnostic tests are designed to detect multiple analytes. The addition of multi-analyte tests to a multi-test algorithm complicates the interpretation of results and increases the potential for misinterpretation by both laboratorians and healthcare providers. Lack of clarity in results reporting can lead to incomplete testing, the misinterpretation of results by healthcare providers, unnecessary additional testing, delays in care for infected persons and inaccurate estimates of disease burden. In most cases, assay-specific software determines the result and interpretation of each individual assay.

In this document, we have adopted the term "laboratory algorithm interpretation" to represent the interpretation that

should be provided for the HIV diagnostic multi-test algorithm. If the algorithm has not been completed for a specimen and the laboratory algorithm interpretation cannot yet be determined, the laboratory report for that specimen should state that test results are pending and recommend that additional tests should be performed to establish the laboratory algorithm interpretation. We strongly suggest that all laboratories that perform testing following the HIV Laboratory Diagnostic Testing Algorithm[1, 7] adopt the reporting language suggested in this document.

Considerations for Persons Taking Antiretrovirals

In recent years, there has been an increase in the number of patients who initiate antiretroviral therapy (ART) earlier in the course of their infection. Starting antiretroviral therapy earlier can also impact the development of HIV specific antibodies, which in turn can impact the ability of some diagnostic assays to detect HIV infection as expected.[8, 9] Therefore, the individual assay results and the laboratory algorithm interpretation need to be considered in the context of the individual's clinical circumstances, including early ART. Likewise, if someone becomes infected while taking antiretrovirals administered for PrEP, the ability of diagnostic tests to detect the infection may be affected.[10] In fact, CDC recommends simultaneous use of both an HIV antibody/antigen assay and an HIV RNA assay when testing a patient with a known history of PrEP use.[6] Under ideal circumstances, laboratories would collect information regarding patient use of PrEP and utilize the recommended testing sequences specific to PrEP, however this information is not always available to the laboratory. Therefore, if test results fluctuate between detectable and undetectable upon repeated testing of the same individual, the laboratory should consider contacting the submitter for more information. Laboratories may also consider including a note on all negative test reports stating, "Antiretroviral drugs taken for treatment or prophylaxis may limit the ability of diagnostic tests to detect HIV infection."

Updates Related to Supplemental Assays

In October 2020, the VioOne™ HIV Profile™ Supplemental Assay was FDA-approved for confirmation of antibodies to HIV-1 and HIV-2. Previously, the Geenius™ HIV 1/2 Supplemental Assay had been the only supplemental test approved for this purpose. The VioOne™ HIV Profile™ Supplemental Assay is an enzyme-linked immunosorbent assay that binds HIV-1/2 antibodies using microplate wells individually coated with one of six antigens (five HIV-1 and one HIV-2). One strip, containing eight wells (the six antigens and two no antigen controls) is used per specimen, and labeled HIV-1 and HIV-2 antigens are used to detect bound antibodies in each well. Absorbance values are read using any microplate reader capable of transmitting light at 450nm +/- 5nm. Negative and positive serum controls must be tested (a strip of each) in each run and a manual calculation based on the average of the negative serum control wells is used to calculate the cutoff value. Specimen wells are considered reactive when the calculated signal to cutoff ratio (S/CO) is greater than one (i.e., the absorbance is greater than the cutoff value). Confirmation of HIV-1 infection requires reactivity in more than two of four HIV-1 antigen containing wells (one of the five HIV-1 antigen containing well is used as an internal control) and HIV-2 infection is confirmed when the well coated with HIV-2 antigen is reactive. Reporting of the VioOne™ HIV Profile™ Supplemental Assay is further addressed in **VioOne™ HIV Profile™ Results Interpretation (page 9)**.

Updates Related to Nucleic Acid Amplification Tests

An HIV nucleic acid amplification test (NAAT) should be used as the third step of the laboratory testing algorithm when the initial screening antibody/antigen test is reactive and the HIV antibody differentiation assay is negative or indeterminate for HIV-1 and/or HIV-2.[1] Although the HIV laboratory testing algorithm has not changed in terms of recommended testing sequence, three recently FDA-approved NAATs have created new considerations when it comes to reporting of laboratory results. The cobas® HIV-1/HIV-2 Qualitative test is the first and only FDA-approved NAAT that detects and differentiates both HIV-1 and HIV-2 RNA. Infection with HIV-2 is rare in the United States and, due to

lack of availability, HIV-2 NAATs had not been previously addressed in diagnostic testing algorithms. However in 2023, CDC released *Technical Update for HIV Nucleic Acid Tests Approved for Diagnostic Purposes*,[5] which updated the HIV laboratory testing algorithm to include an option for use of an HIV-1/HIV-2 NAAT in the third step of the testing sequence.

CDC's *Technical Update*[5] addresses additional assays including the Aptima® HIV-1 Quant Dx assay and the Alinity m HIV-1 Assay, the first dual claim assays for HIV. With the dual claim, both tests can be used for diagnosis (i.e., with a qualitative result) as well as clinical management (i.e., with a quantitative result) of HIV-1 infection. It is important to recognize that while serum and plasma are acceptable specimen types for qualitative diagnostic use, plasma is the only acceptable specimen type for quantitative testing. When establishing laboratory specific testing algorithms and specimen processing protocols, this should be taken into consideration. If quantitative viral load results will be reported on samples with detected HIV-1, plasma will be needed for testing. Additionally, both dual claim assays allow for dilution of plasma in order to obtain quantitative results, however specimens should not be diluted when testing for diagnostic purposes.

CDC and APHL have not changed the recommendation that laboratories perform an HIV-1/HIV-2 antibody differentiation supplemental immunoassay as the second step after a reactive antigen/antibody screening immunoassay.[11] However, CDC's *Technical Update* does provide guidance on how HIV NAATs with diagnostic claims can be used in the second step of the diagnostic testing algorithm, as there are circumstances where this approach makes sense. These circumstances include symptoms coinciding with a known or suspected recent exposure and rare situations where individuals have participated in vaccine or neutralizing antibody prevention trials. Although the reporting of NAAT is mostly straightforward, this document will address new considerations that arise with the use of HIV NAATs with diagnostic claims.

Reporting Geenius™ Results

Overall Comments

The Geenius™ HIV 1/2 Supplemental Assay cassette contains six test bands (four HIV-1 and two HIV-2 bands) to detect HIV-1 and/or HIV-2 antibodies and a control band. The Geenius™ reader equipped with assay-specific software analyzes the signals for each band to produce the individual results for HIV-1 and HIV-2, which are combined to provide the conclusion or **Final Assay Interpretation**. The Geenius™ reader automatically produces a printable report at the completion of every test (**Figure 1**) which includes the conclusion and the individual results for HIV-1 and HIV-2 in parenthetical notation. While this file can be printed for recordkeeping purposes, most laboratories extract the relevant information from it to create their own laboratory report.

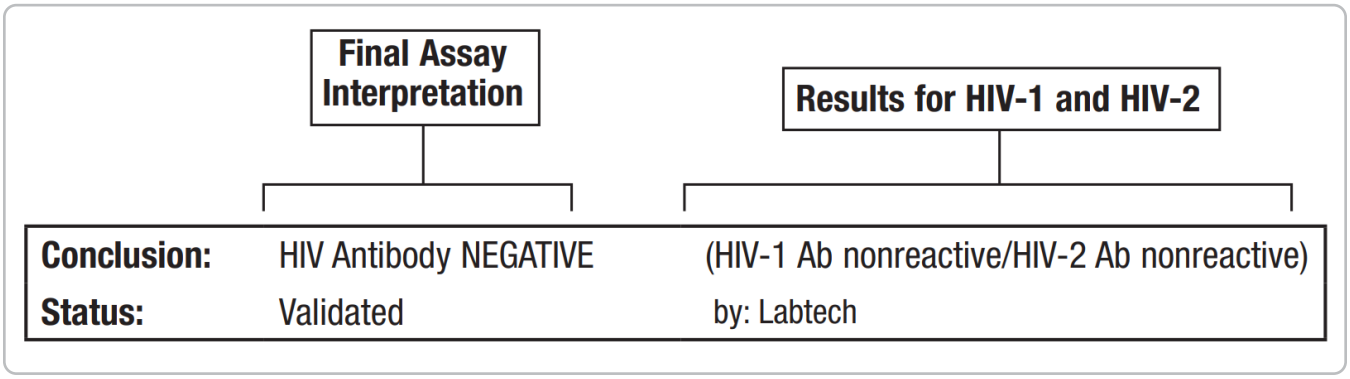
In the updated package insert from September 2017, Bio-Rad provided clarification on which components from the Geenius™ test report should be communicated to the ordering provider. The revised package insert states in bold font that, "The **Final Assay Interpretation** should always be reported to the ordering provider." Therefore, all laboratories reporting Geenius™ results to healthcare providers and public health surveillance programs should always report the **Final Assay Interpretation** (also referred to as the "Conclusion" on the Geenius™ report) as determined by the Geenius™ software.

Reporting of the individual results for HIV-1 and HIV-2 by the laboratory is not specifically prohibited by the manufacturer,[5] but it is our recommendation that laboratories do not report this information. The individual results for HIV-1 and HIV-2 are combined with the relative strength of the signals to produce the **Final Assay Interpretation**. The performance characteristics of the Geenius™ assay that appear in the package insert are based on the **Final Assay Interpretation** and not the individual results for HIV-1 and HIV-2; this point is clarified in the "Limitations" section of the revised package insert. Therefore, the individual results should not be used for diagnostic purposes because they may provide misleading information.

In addition, while band patterns are present on the Geenius™ instrument printable test report, we strongly recommend that laboratories do not report the band patterns. Information is not available regarding any correlation of banding pattern to stage of disease and, therefore, should not be used for diagnostic purposes or disease staging.

In summary, we recommend that all laboratories include the Geenius™ Final Assay Interpretation on the laboratory report. We also recommend that laboratories exclude the individual results for HIV-1 and HIV-2 from the Geenius™ Assay on the laboratory report.

Figure 1: Image from Geenius™ Package Insert of Report from Reader.[12]



Geenius™ Final Assay Interpretations

In the updated Geenius™ package insert,[11] explanatory notes for each combination of individual HIV-1 and HIV-2 results and corresponding **Final Assay Interpretation** have been added. The package insert, together with the updated *Quick Reference Guide*[7] and this document provide clarification on how to proceed in each situation. However, three of the Geenius™ assay results (**Final Assay Interpretations**) may cause confusion, so we have provided further information for consideration. These results and their interpretation in the testing algorithm can be found in **Table 1 (page 13)**.

HIV-2 Positive with HIV-1 Cross-reactivity

The **Final Assay Interpretation** of "**HIV-2 with HIV-1 Cross-reactivity**" should be considered equivalent to the **Final Assay Interpretation** of "**HIV-2 Positive**." In both cases the Geenius™ software has detected reactivity to HIV-2 antibodies. In the former case, it has also detected reactivity to HIV-1 but the HIV-1 reactivity does not meet the criteria to be considered positive. This pattern is indicative of cross-reactivity of the HIV-2 antibodies with the HIV-1 antigens and is not sufficient to be considered HIV-1 Positive. This **Final Assay Interpretation** is distinct from "**HIV Positive Untypable**," in which the criteria for both HIV-1 Positive and HIV-2 Positive were met, where the HIV-1 and HIV-2 antibodies are strong enough for the individual results for HIV- 1 and HIV-2 to be considered positive and which would indicate the possibility of a dual infection with HIV-1 and HIV-2.

Specimens with the **Final Assay Interpretation** "**HIV-2 with HIV-1 Cross-reactivity**" do not require any additional testing. Persons with this **Final Assay Interpretation** should be provided appropriate counseling and linked to medical care.

HIV-2 Indeterminate

Specimens with the **Final Assay Interpretation** "**HIV-2 Indeterminate**" require additional testing. The first step is to repeat Geenius™ testing with the same specimen on a new cartridge. If upon repeat testing the **Final Assay Interpretation** is:

- **HIV-1 Positive *or* HIV-2 Positive:** This result should be reported as the **Final Assay Interpretation** for Geenius™ and no further testing is needed.
- **HIV Antibody Negative:** This result should be reported as the **Final Assay Interpretation** for Geenius™ and testing with an HIV-1 NAAT is indicated.
- **HIV-2 Indeterminate:** This result should be reported as the **Final Assay Interpretation** for Geenius™ and an HIV-1 NAAT should be conducted.

The following recommendations should be considered based on the HIV-1 NAAT results:

- **If HIV-1 RNA is detected:** The laboratory algorithm interpretation would be "**Positive for HIV-1, laboratory evidence of HIV-1 infection consistent with an acute HIV-1 infection**" and the person should be provided with appropriate counseling and linked to medical care.
- **If HIV-1 RNA is not detected:** The sample should be referred for testing with a validated supplemental HIV-2 test (antibody test or NAAT), if available. Alternatively, the laboratory report may recommend repeating the algorithm with a new specimen in two to four weeks to assess HIV-2 infection. Supplemental HIV-2 testing may be available through commercial laboratories, public health laboratories or CDC.

HIV Indeterminate

Specimens with the **Final Assay Interpretation** "**HIV Indeterminate**" should prompt the same testing sequence and recommendations as described above for a repeat "HIV-2 Indeterminate" **Final Assay Interpretation**, i.e., an HIV-1 NAAT should be conducted.

- **If HIV-1 RNA is detected:** The laboratory algorithm interpretation would be "**Positive for HIV-1, laboratory evidence of HIV-1 infection consistent with an acute HIV-1 infection**," and the person should be provided with appropriate counseling and linked to medical care.
- **If HIV-1 RNA is not detected:** The sample should be referred for testing with a validated supplemental HIV-2 test (antibody test or NAAT), if available. Alternatively, the laboratory report may recommend repeating the algorithm with a new specimen in two to four weeks to assess HIV-2 infection. Supplemental HIV-2 testing may be available through commercial laboratories, public health laboratories or CDC.

Reporting VioOne™ HIV Profile™ Results

Overall Comments

The VioOne™ HIV Profile™ Supplemental Assay requires manual calculation of the cutoff value and manual determination of test results. Accordingly, HIV Profile™ assay users must manually determine which runs or samples yield invalid results. The package insert states that invalid results should not be reported. Instead, specimens should be retested.

A test run is invalid and all specimens should be retested when:

- Two or more negative serum control wells have an absorbance > 0.2 or fall outside of the calculated range.
- Upon final calculation, the mean of the negative serum control wells is > 0.1.
- The signal to cutoff ratio for any well containing the positive serum control falls outside of expected ranges.

A specimen is considered invalid and should be retested when:

- The absorbance of the no viral antigen well (Well A) is > the calculated cutoff value.
- A reactive result is obtained in the HIV-1 reduced gp160 well (Well C) and a non-reactive result is obtained for the HIV-1 gp160 well (Well D).
- A reactive result in the HIV-1 reduced gp160 well (Well C) is greater than a reactive result in the HIV-1 gp160 well (Well D).

The test's package insert includes a **Results Interpretation Guide** that uses the terms "**Test Results**" and "**Results Interpretation**." The "Test Results" are described as either reactive or nonreactive to HIV-1 or HIV-2 antigens, but the VioOne™ HIV Profile™ Supplemental Assay detects antibodies to HIV-1 and HIV-2 that may be present in a patient's serum or plasma. This is an issue of semantics, as the specimen is reactive or nonreactive to the antigens in the assay due to the presence or absence of HIV1/2 antibodies. Unlike the Geenius™ assay, the VioOne™ HIV Profile™ Supplemental Assay package insert does not specifically state whether test results, **Results Interpretation**, or both should be reported.

We recommend that all laboratories include the appropriate HIV Profile™ **Results Interpretation** on the laboratory report (**Figure 2, page 10**), and would encourage laboratories to consider addition of the word antibody (e.g., HIV antibody Negative). We strongly recommend that laboratories exclude the individual "test results" for HIV-1 and HIV-2 from the HIV Profile™ Assay on the laboratory report, especially because this may lead to confusion regarding reactivity to antigens versus reactivity for antibodies. When HIV-1 reactivity is observed we also strongly recommend that laboratories do not include information regarding which antigens were reactive.

VioOne™ HIV Profile™ Results Interpretation

The VioOne™ HIV Profile™ Supplemental Assay package insert, together with this document, provide clarification on how to proceed with the battery of possible results. However, three of the HIV Profile™ assay results may cause confusion, so we have provided further information for consideration.

HIV-1 Positive with Reactivity to HIV-2 Antigen

When the test result is "**Reactive for 2 or more HIV-1 Ags**" and "**Reactive for HIV-2 Ag**" the specimen meets the positivity criteria for both HIV-1 and HIV-2 and the **Results Interpretation** depends on the signal to cutoff ratio of the individual wells. When the S/CO of the HIV-1 gp41 well (Well E) is greater than the S/CO of the HIV-2 gp36 well (Well H), the **Results Interpretation** is "**HIV-1 positive with reactivity to HIV-2 Antigen.**" This **Results Interpretation** does not exclude the possibility of a (rare) HIV-1 and HIV-2 co-infection.

HIV-2 Positive with Reactivity to HIV-1 Antigens

When the test result is "**Reactive for 2 or more HIV-1 Ags**" and "**Reactive for HIV-2 Ag**" the specimen meets the positivity criteria for both HIV-1 and HIV-2 and the **Results Interpretation** depends on the signal to cutoff ratio of the individual wells. When the S/CO of the HIV-1 gp41 well (Well E) is less than or equal to the S/CO of the HIV-2 gp36 well (Well H), the **Results Interpretation** is "**HIV-2 positive with reactivity to HIV-1 Antigen.**" This **Results Interpretation** does not exclude the possibility of a (rare) HIV-1 and HIV-2 co-infection. However, HIV-2 specimens are known to show a high level of cross-reactivity to HIV-1 antigens in the VioOne™ HIV Profile™ Supplemental Assay.

HIV-1 Indeterminate

Specimens that are reactive for one HIV-1 antigen only yield the **Results Interpretation** of "**HIV-1 Indeterminate.**" Either early seroconversion or cross-reactivity with other retroviruses could yield this result. This should prompt the same testing sequence and recommendations as a HIV-1 Indeterminate Geenius™ **Final Assay Interpretation** (i.e., an HIV-1 NAAT should be conducted). If HIV-1 RNA is detected, the laboratory algorithm interpretation would be "**Positive for HIV-1, laboratory evidence of HIV-1 infection consistent with an acute HIV-1 infection,**" and the person should be provided with appropriate counseling and linked to medical care.

Figure 2. **Results Interpretation Guide table from HIV Profile™ package insert.**[13]

Cat.	Test Results		Results Interpretation	
	HIV-1 Antigens	**HIV-2 Antigen**	**Interpretation**	**Symbol**
1	Nonreactive[1] for all HIV-1 Ags[2]	Nonreactive for HIV-2 Ag	**HIV Negative**	**NEG**
2	Reactive[1] for 1 HIV-1 Ag only	Nonreactive for HIV-2 Ag	**HIV-1 Indeterminate**	**HIV-1 IND**
3	Reactive for 2 or more HIV-1 Ags	Nonreactive for HIV-2 Ag	**HIV-1 Positive**	**HIV-1 POS**
4	Reactive for 1 or no HIV-1 Ag(s)	Reactive for HIV-2 Ag	**HIV-2 Positive**	**HIV-2 POS**
5	Reactive for 2 or more HIV-1 Ags	Reactive for HIV-2 Ag	a. **HIV-1 Positive with Reactivity to HIV-2 Antigen** (HIV-1 gp41 S/CO > HIV-2 gp36 S/CO) b. **HIV-2 Positive with Reactivity to HIV-1 Antigens** (HIV-1 gp41 S/CO ⩽ HIV-2 gp36 S/CO)	**HIV-1 POS***[3] **HIV-2 POS***[3]

Interpretation Table legend:

1. Nonreactive: signal to cutoff ratio (S/CO) is less than 1.0; Reactive: S/CO ≥ 1.0
2. Ags: antigens
3. This test result does not exclude the possibility of an HIV-1 and HIV-2 coinfection (rare).

Reporting HIV Nucleic Acid Testing

Overall Comments

In accordance with the *Technical Update for HIV Nucleic Acid Tests Approved for Diagnostic Purposes*, the guidance in **Table 1 (page 13)** and the **HIV Laboratory Testing Algorithms (page 19)** in the **Appendix** (**Figure 6, page 20**, **Figure 7, page 21** and **Figure 8, page 22**) have been updated to include HIV-1/-2 NAAT testing. It is important to recognize the ability to confirm HIV-1 and/or HIV-2 when choosing and utilizing these assays for diagnostic purposes. **Figure 7** outlines a testing sequence that utilizes an HIV NAAT assay as the second step of the diagnostic algorithm but does not address patients on PrEP. In this algorithm, when specimens are HIV-1/-2 antigen/antibody combination assay positive and yield a HIV NAAT result of HIV RNA not detected, HIV-1/HIV-2 antibody differentiation immunoassay testing should be performed as the third step of the diagnostic algorithm.

Updates to reporting of nucleic acid testing in this document are driven primarily by the availability and FDA clearance of the cobas®HIV-1/HIV-2 Qualitative test, the Aptima® HIV-1 Quant Dx and the Alinity m HIV-1 Assay. While these assays have distinct differences that will be discussed below, commonalities include the use of automated systems for testing and result reporting. All three tests are run on platforms that utilize automated data management systems so that samples are automatically marked as invalid upon failure of internal or external controls. When valid results are produced, all three platforms will display a clear result. All three assays also utilize internal controls and dual targets for HIV-1 with no discrimination of HIV-1 groups or subtypes.

When NAAT testing is conducted as part of the diagnostic testing algorithm, we recommend that laboratories report the result of the individual NAAT assay targets using the terms detected or not detected, along with the laboratory algorithm interpretation as shown in **Table 1 (page 13)**. As applicable, quantitative results may be provided for plasma specimens, but serum cannot be used to obtain quantitative results.[14]

HIV NAAT Results Interpretation

cobas®HIV-1/HIV-2 Qualitative Assay

The cobas®HIV-1/HIV-2 Qualitative assay is a fully automated reverse transcription PCR that detects and differentiates HIV-1 and HIV-2. Data analysis is performed by the cobas® 5800/6800/8800 software, which assigns test results for all tests as non-reactive, reactive or invalid. These results can be reported using the interpretations found in a **Results Interpretation** table in the test's package insert (**Figure 3**), which align with those in **Table 1 (page 13)**.

Figure 3: Results Interpretation Guide table from cobas®HIV-1/HIV-2 Qualitative assay package insert.[15]

Valid	Overall Result	Target 1	Target 2	Interpretation
Yes	**Reactive**	HIV-1 Reactive	HIV-2 Reactive	All requested results were valid. Target signal detected for HIV-1 and HIV-2.
Yes	**Reactive**	HIV-1 Reactive	HIV-2 Non-Reactive	All requested results were valid. Target signal detected for HIV-1. No target signal detected for HIV-2.
Yes	**Reactive**	HIV-1 Non-Reactive	HIV-2 Reactive	All requested results were valid. No target signal detected for HIV-1. Target signal detected for HIV-2.
Yes	**Non-Reactive**	HIV-1 Non-Reactive	HIV-2 Non-Reactive	All requested results were valid. No target signal detected for HIV-1 or HIV-2.
No	**Invalid**	Invalid	Invalid	Both HIV-1 and HIV-2 results are invalid. Original specimen should be re-tested to obtain valid HIV-1 and HIV-2 results. If the results are still invalid, a new specimen should be obtained.

Aptima® HIV-1 Quant Dx Assay

The Aptima® HIV-1 Quant Dx assay is a fully automated transcription-mediated amplification assay that detects HIV-1 in plasma and serum. The Aptima HIV-1 Quant Dx assay targets both HIV-1 pol and LTR independently and the reported result is based on pol. If pol is not amplified, the system will report the result from LTR. Data analysis is performed by the Panther system software, which assigns quantitative test results for all tests as not detected, <30 detected, or a numerical value corresponding to the HIV-1 RNA concentration in the specimen. The package insert specifically states that the reported result is to be provided by the Panther system software, as that is what was used for clinical validation. However, operators must interpret the results into a qualitative result using a table provided in the package insert and shown below (**Figure 4**). Quantitative results must not be reported for serum specimens.

Figure 4: **Results Interpretation Guide table from Aptima® HIV-1 Quant Dx package insert.**[16]

Reported Aptima HIV-1 Quant Dx Assay Result		HIV-1 RNA Concentration Interpretation	User's Diagnostic Qualitative Interpretation[c]
Copies /mL[a]	Log_{10} Value[b]		
Not Detected	Not Detected	HIV-1 RNA not detected.	Non-reactive for HIV-1 RNA
<30 detected[e]	<1.47	HIV-1 RNA is detected but at a level below the LLoQ.	Reactive for HIV-1 RNA
30 to 10,000,000	1.47 to 7.00	HIV-1 RNA concentration is within the linear range of 30 to 10,000,000 copies/mL.	Reactive for HIV-1 RNA
>10,000,000	>7.00	HIV-1 RNA concentration is above the upper limit of quantitation (ULoQ).	Reactive for HIV-1 RNA
Invalid[d]	Invalid[d]	There was an error in the generation of the result. Specimen should be retested.	Invalid

[a] The conversion factor for copies to International Unit (IU) for the 3rd International Standard for HIV-1 RNA (10/152) is 0.35 copies/IU.
[b] Value is truncated to two decimal places.
[c] A diagnostic interpretation may be made from either serum or plasma specimens that have not been diluted.
[d] Invalid results are displayed in blue-colored font.
[e] The software's lowest reportable value is 30 copies/mL. The assay's highest LoD is 17.5 copies/mL for subtype G. For LoD values of all subtypes, see Table 3. The LoD using the WHO 3rd International Standard (subtype B) for HIV-1 RNA is 12.1 copies/mL (see Table 2).

Alinity m HIV-1 Assay

The Alinity m HIV-1 Assay is a fully automated reverse transcription PCR that detects HIV-1 in plasma and serum. Data analysis is performed by the Alinity m System, which reports qualitative results for serum and assigns quantitative test results and interpretation for plasma specimens. Qualitative results are reported as positive or negative and quantitative results and interpretations are shown in **Figure 5 (page 12)**.

Figure 5: **Results Interpretation Guide table from Alinity m HIV-1 Assay package insert.**[17]

Alinity m System Reported	
Result	**Interpretation**
Not Detected	Target not detected
< LLoQ	Detected < LLoQ
20 Copies/mL to ≤ ULoQ (1.30 Log Copies/mL to ≤ ULoQ)	Detected and quantified
> ULoQ	> ULoQ[a]

[a] Specimens tested neat or with 1:2.5 dilution procedure that have >ULoQ interpretation may be retested using the 1:50 dilution procedure to determine a result within the quantitation range.

Laboratory Reporting Guidance

Reporting Results for Serum and Plasma Specimens

Table 1: Guidance for Reporting Results from the HIV Laboratory Diagnostic Testing Algorithm for Serum and Plasma Specimens[a]

Test Sequence Outcomes				Outcome Interpretations and Actions		
Step 1[b]	Step 2[c]	Step 3[d]		Laboratory Algorithm Interpretation[e]	Interpretation for Provider Use[f]	Further Actions[g]
HIV-1/ HIV-2 Ag/Ab IA	HIV-1/HIV-2 Antibody Differentiation IA	HIV-1 NAAT	HIV-1/-2 NAAT			
Nonreactive	n/a	n/a	n/a	HIV-1 antigen and HIV-1/HIV-2 antibodies were not detected. No laboratory evidence of HIV infection.	HIV Negative	If recent HIV exposure is suspected or reported: • Conduct HIV-1 or HIV-1/-2 NAAT or request a new specimen. **AND** • Repeat the algorithm according to CDC Guidelines.[h]
Reactive	HIV-1 Positive	n/a	n/a	Positive for HIV-1 antibodies. Laboratory evidence of HIV-1 infection is present.	HIV-1 Positive	Link patient to HIV medical care and provide appropriate prevention counseling.[i]
Reactive	HIV-2 Positive	n/a	n/a	Positive for HIV-2 antibodies. Laboratory evidence of HIV-2 infection is present.	HIV-2 Positive	Link patient to HIV medical care and provide appropriate prevention counseling.[i]
Reactive	HIV-2 Positive with HIV-1 cross reactivity (Geenius™)	n/a	n/a	Positive for HIV-2 antibodies. Laboratory evidence of HIV-2 infection is present.	HIV-2 Positive. This result is distinct from HIV positive untypable.	Link patient to HIV medical care and provide appropriate prevention counseling.[i]

a Please note that the tests outlined in Table 1 are not FDA-approved for oral fluid or dried blood spots.

b In **Step 1**, the need for repeating a screening immunoassay (IA) following an initial reactive test is assay dependent; refer to product package insert.

c **Step 2** contains the **Final Assay Interpretation** per the Geenius™ and/or **Results Interpretations** per the HIV Profile™ assay package insert, as applicable. We recommend excluding the individual HIV-1 and HIV-2 results on the laboratory report and using the word "antibody" when reporting a negative result. If individual HIV-1 /HIV-2 results are used, the Geenius™ **Final Assay Interpretation** or HIV Profile™ **Results Interpretation** should also be included.

d **Step 3** applies to HIV NAAT assays that have been approved for diagnostic testing.

e The **Laboratory Algorithm Interpretation** column contains suggested language to be used for the laboratory report and it can be directly used for reporting from LIMS systems.

f The **Interpretation for Provider Use** column contains simplified language of the previous column, "Laboratory Algorithm Interpretation," and is included here for healthcare providers or other non-laboratorians that may also use this table as a reference document. This does not need to be included on the laboratory report.

g Comments under "**Further Action**" can be included as language in the laboratory report or can be used as guidance for laboratorians to discuss test results with healthcare providers or health department staff.

h Please refer to the CDC Laboratory Guidance, available at: stacks.cdc.gov/view/cdc/38856

i Please refer to the CDC HIV Guidelines and Recommendations to find the most appropriate information by age and risk group for the patient in question. Available at: www.cdc.gov/hivpartners/php/guidelines/?CDC_AAref_Val=https://www.cdc.gov/hiv/guidelines/

Test Sequence Outcomes				Outcome Interpretations and Actions		
Step 1[b]	Step 2[c]	Step 3[d]		Laboratory Algorithm Interpretation[e]	Interpretation for Provider Use[f]	Further Actions[g]
HIV-1/ HIV-2 Ag/Ab IA	HIV-1/HIV-2 Antibody Differentiation IA	HIV-1 NAAT	HIV-1/-2 NAAT			
Reactive	HIV-1 Positive with reactivity to HIV-2 antigen (HIV Profile™)	n/a	n/a	Positive for HIV-1 antibodies. Laboratory evidence of HIV-1 infection is present.	HIV-1 Positive	• Link patient to HIV medical care and provide appropriate prevention counseling.[i] • Provider may consider additional testing for HIV-1 RNA or DNA and HIV-2 RNA or DNA to verify or rule out HIV-1/HIV-2 dual infection.
Reactive	HIV-2 Positive with reactivity to HIV-1 Antigen (HIV Profile™)	n/a	n/a	Positive for HIV-2 antibodies. Laboratory evidence of HIV-2 infection is present.	HIV-2 Positive	• Link patient to HIV medical care and provide appropriate prevention counseling.[i] • Provider may consider additional testing for HIV-1 RNA or DNA and HIV-2 RNA or DNA to verify or rule out HIV-1/HIV-2 dual infection.
Reactive	HIV Positive untypable (Geenius™)	n/a	n/a	Positive for HIV-1 and HIV-2 antibodies. Laboratory evidence of HIV-1 and/or HIV-2 infection is present.	HIV Positive	• Link patient to HIV medical care and provide appropriate prevention counseling.[i] • Provider may consider additional testing for HIV-1 RNA or DNA and HIV-2 RNA or DNA to verify or rule out HIV-1/HIV-2 dual infection. • Request additional specimen if original specimen volume is insufficient.
Reactive	• HIV-1 indeterminate **OR** • HIV-2 indeterminate[j] **OR** • HIV indeterminate	Detected	• HIV-1 NAAT **detected** **AND** • HIV-2 NAAT **not detected**	**Positive for HIV-1.** Laboratory evidence of HIV-1 infection consistent with an **acute HIV-1 infection.** If plasma was tested in a dual claim NAAT, provide a quantitative result.	**Acute** HIV-1 Positive	Link patient to HIV medical care and provide appropriate prevention counseling immediately[i] to expedite prevention practices.
Reactive	• HIV-1 indeterminate **OR** • HIV-2 indeterminate[j] **OR** • HIV indeterminate	n/a	• HIV-1 NAAT **detected** **AND** • HIV-2 NAAT **detected**	**Positive for and HIV-1 and HIV-2.** Laboratory evidence of HIV-1 and HIV-2 infection consistent with an **acute HIV-1 and HIV-2 infection**.	**Acute** HIV-1 and HIV-2 Positive	Link patient to HIV medical care and provide appropriate prevention counseling immediately[i] to expedite prevention practices.

j Follow Geenius™ package insert and refer to the CDC Technical Update. Available at: stacks.cdc.gov/view/cdc/40790

Test Sequence Outcomes				Outcome Interpretations and Actions		
Step 1[b]	Step 2[c]	Step 3[d]		Laboratory Algorithm Interpretation[e]	Interpretation for Provider Use[f]	Further Actions[g]
HIV-1/ HIV-2 Ag/Ab IA	HIV-1/HIV-2 Antibody Differentiation IA	HIV-1 NAAT	HIV-1/-2 NAAT			
Reactive	• HIV-1 indeterminate **OR** • HIV-2 indeterminate[j] **OR** • HIV indeterminate	n/a	• HIV-1 NAAT **not detected** **AND** • HIV-2 NAAT **detected**	**Positive for HIV-2.** Laboratory evidence of HIV-2 infection consistent with an **acute HIV-2 infection**.	**Acute** HIV-2 Positive	Link patient to HIV medical care and provide appropriate prevention counseling immediately[i] to expedite prevention practices.
Reactive	HIV-1 Indeterminate	n/a	• HIV-1 NAAT **not detected** **AND** • HIV-2 NAAT **not detected**	HIV antibodies were not confirmed and HIV-1/2 RNA was not detected.	HIV Negative	If recent HIV exposure is suspected or reported, request a new specimen and repeat the algorithm according to CDC guidance.[h]
Reactive	HIV-1 Indeterminate	Not detected	n/a	HIV-1 antibodies were not confirmed and HIV-1 RNA was not detected.	HIV Negative	If recent HIV exposure is suspected or reported, request a new specimen and repeat the algorithm according to CDC guidance.[h]
Reactive	HIV-2 Indeterminate[j] (Geenius™)	n/a	• HIV-1 NAAT **not detected** **AND** • HIV-2 NAAT **not detected**	HIV antibodies were not confirmed and HIV-1/2 RNA was not detected.	HIV Negative	If recent HIV exposure is suspected or reported, request a new specimen and repeat the algorithm according to CDC guidance.[h]
Reactive	• HIV-2 Indeterminate[j] (Geenius™) **OR** • HIV Indeterminate	Not detected	n/a	HIV-1 antibodies were not confirmed and HIV-1 RNA was not detected. HIV-2 inconclusive.	HIV-1 Negative, HIV-2 Inconclusive	Refer specimen for testing with a nucleic acid amplification assay. If recent HIV exposure is suspected or reported, request a new specimen and repeat the algorithm according to CDC guidance.[h]
Reactive	HIV Indeterminate	n/a	• HIV-1 NAAT **not detected** **AND** • HIV-2 NAAT **not detected**	HIV antibodies were not confirmed and HIV-1/-2 RNA was not detected.	HIV Negative	If recent HIV exposure is suspected or reported, request a new specimen and repeat the algorithm according to CDC guidance.[h]
Reactive	HIV Antibody Negative	Detected	• HIV-1 NAAT **detected** **AND** • HIV-2 NAAT **not detected**	Positive for HIV-1. Laboratory evidence of HIV-1 infection consistent with an **acute** HIV-1 infection. If plasma was tested in a dual claim NAAT, provide a quantitative result.	**Acute** HIV-1 Positive	Link patient to HIV medical care and provide appropriate prevention counseling[i] immediately to expedite prevention practices.
Reactive	HIV Antibody Negative	Not detected	• HIV-1 NAAT **not detected** **AND** • HIV-2 NAAT **detected**	Positive for HIV-2. Laboratory evidence of HIV-2 infection consistent with an **acute** HIV-2 infection.	**Acute** HIV-2 Positive	Link patient to HIV medical care and provide appropriate prevention counseling[i] immediately to expedite prevention practices.

Test Sequence Outcomes				Outcome Interpretations and Actions		
Step 1[b]	Step 2[c]	Step 3[d]		Laboratory Algorithm Interpretation[e]	Interpretation for Provider Use[f]	Further Actions[g]
HIV-1/ HIV-2 Ag/Ab IA	HIV-1/HIV-2 Antibody Differentiation IA	HIV-1 NAAT	HIV-1/-2 NAAT			
Reactive	HIV Antibody Negative	Not detected	• HIV-1 NAAT **not detected** **AND** • HIV-2 NAAT **not detected**	HIV antibodies were not confirmed and HIV1/-2 RNA was not detected.	HIV Negative	If recent HIV exposure is suspected or reported, request a new specimen and repeat the algorithm according to CDC guidance.[h]
Reactive	HIV Antibody Negative or Indeterminate	Invalid or not performed	Invalid or not performed	Inconclusive	Inconclusive	• Request an additional specimen and repeat the algorithm. • Ensure HIV-1 NAAT is performed, if indicated by results of HIV-1/HIV-2 Ag/Ab IA and HIV-1/HIV-2 Ab differentiation IA.[i]

Reporting Test Results to Healthcare Providers

All laboratory reports should include the results for all tests performed, as well as a laboratory algorithm interpretation of the HIV Laboratory Testing Algorithm. Health care providers may be receiving results from one or more laboratories. If the laboratory that reports the results to the provider did not conduct all of the tests, this laboratory may not have access to other results and may not be able to provide a laboratory algorithm interpretation. This reporting language document can be used as a resource to help identify the laboratory algorithm interpretation when results are received from multiple laboratories.

Table 1 (page 13) includes an "Interpretation for Provider Use" column, which is a shortened and simplified version of the laboratory algorithm interpretation. The information does not need to be included on the laboratory report, but it may be useful to the provider ordering the testing. Additionally, the "Further Actions" column in the table also can provide help to guide submitters on appropriate next steps following testing.

The HIV Laboratory Testing Algorithm is intended to maximize the identification of new, previously undiagnosed HIV infections. However, laboratories may receive specimens from previously diagnosed individuals, including individuals on ART or PrEP, for the purpose of verifying positive infection status for the medical record. Over time, effective ART may cause antibody titers to decline. Furthermore, ART initiated during acute infection may preclude seroconversion altogether.[8] In such cases, serological tests may be nonreactive or indeterminate and HIV RNA may be undetectable due to ART or PrEP, leading to a false negative result. Laboratories may not be informed of these circumstances when a specimen is submitted for testing. Therefore, including a statement on all laboratory reports indicating that the test results should be interpreted in the context of all clinically relevant information such as current or recent use of antiretrovirals is recommended.

CDC developed *Prexposure prophylaxis for the prevention of HIV Infection in the United States – 2021 Update* to provide clinical practice guidelines, including two laboratory testing algorithms for assessing HIV status:

1. In persons with no history of recent antiretroviral exposure starting (or restarting) PrEP
2. At follow-up visits while persons are taking, or have recently taken, PrEP.[6]

The following are some general guidelines to follow when reporting HIV test results to healthcare providers:

1. Laboratories should specify the assays that were used in HIV testing (see **HIV Laboratory Testing Algorithms, page 19** for links to lists of FDA-approved tests) and provide the recommended results or interpretation for each assay.
2. If laboratories use a testing sequence other than the recommended laboratory algorithm or assays other than those currently recommended, reports should describe the limitations associated with the testing sequence used. Refer to Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations for more information on the limitations associated with alternatives to the recommended algorithm.[1,6]
3. Laboratories may issue preliminary reports containing the result from each test in the algorithm as it becomes available. If the recommended testing algorithm is not completed at that time, laboratories should specify which test results are pending, which additional tests are needed to complete the laboratory algorithm interpretation and recommend any additional testing that may be required. The final report should contain the laboratory algorithm interpretation.
4. Laboratories that refer patient specimens to one or more referral laboratories to perform the algorithm are encouraged to compile the results received from those referral laboratories and transmit all results as a single report to the provider. This action would facilitate clear messaging to the provider. In situations where this is not feasible, these results may be transmitted directly to the provider from multiple testing laboratories. In either case, the healthcare provider should receive a result for each test performed. Where possible and applicable, the

laboratory report should include a laboratory algorithm interpretation and recommendations for appropriate next steps; however, in some reporting scenarios, this may not be practical.

5. The diagnosis of acute HIV infection indicates a potential need for public health interventions due to the increased risk of transmission to uninfected partners during acute infection. Laboratories should have arrangements in place to expedite reporting of test results consistent with acute HIV infection to the healthcare provider and to the health department to help ensure quick access to treatment.

Reporting for Surveillance

All states, the District of Columbia, US territories and dependent areas require that laboratories report test results indicative of HIV infection to the surveillance program in the department of health in the patient's jurisdiction of residence.[18] Specific requirements of each state or local health department might differ; therefore, ensure the specific requirements of your jurisdiction are followed.

All laboratory reports should include the result for all tests performed as well as a laboratory algorithm interpretation of the HIV Laboratory Testing Algorithm that is generated from the combination of assay results. Health department surveillance programs may receive results from a single specimen from one or multiple laboratories. If the laboratory reporting the results did not conduct all tests, the laboratory may not have access to other results and may not be able to provide a laboratory algorithm interpretation. Therefore, the burden of combining these results and determining the laboratory algorithm interpretation for case classification purposes may fall to the surveillance program. The reporting language document can be used as a resource to help identify the laboratory algorithm interpretation when results are received from multiple laboratories.

Table 1 (page 13) includes an "Interpretation for Provider Use" column, which is a shortened and simplified version of the laboratory algorithm interpretation. The information does not need to be included on the laboratory report, but it may be useful to the provider ordering the testing. Additionally, the "Further Actions" column in the table also can provide help to guide submitters on appropriate next steps following testing.

Contact the HIV surveillance coordinator in your jurisdiction for additional information regarding reporting requirements. The National Alliance of State and Territorial AIDS Directors (NASTAD) maintains a contact list for state HIV surveillance coordinators.

CDC has recently developed and published a LOINC (Logical Observation Identifiers Names and Codes) map for all FDA-approved HIV diagnostic tests. The standardized mapping was developed in coordination with APHL, the Regenstrief Institute, Inc. and CDC.

Appendix

HIV Laboratory Testing Algorithms

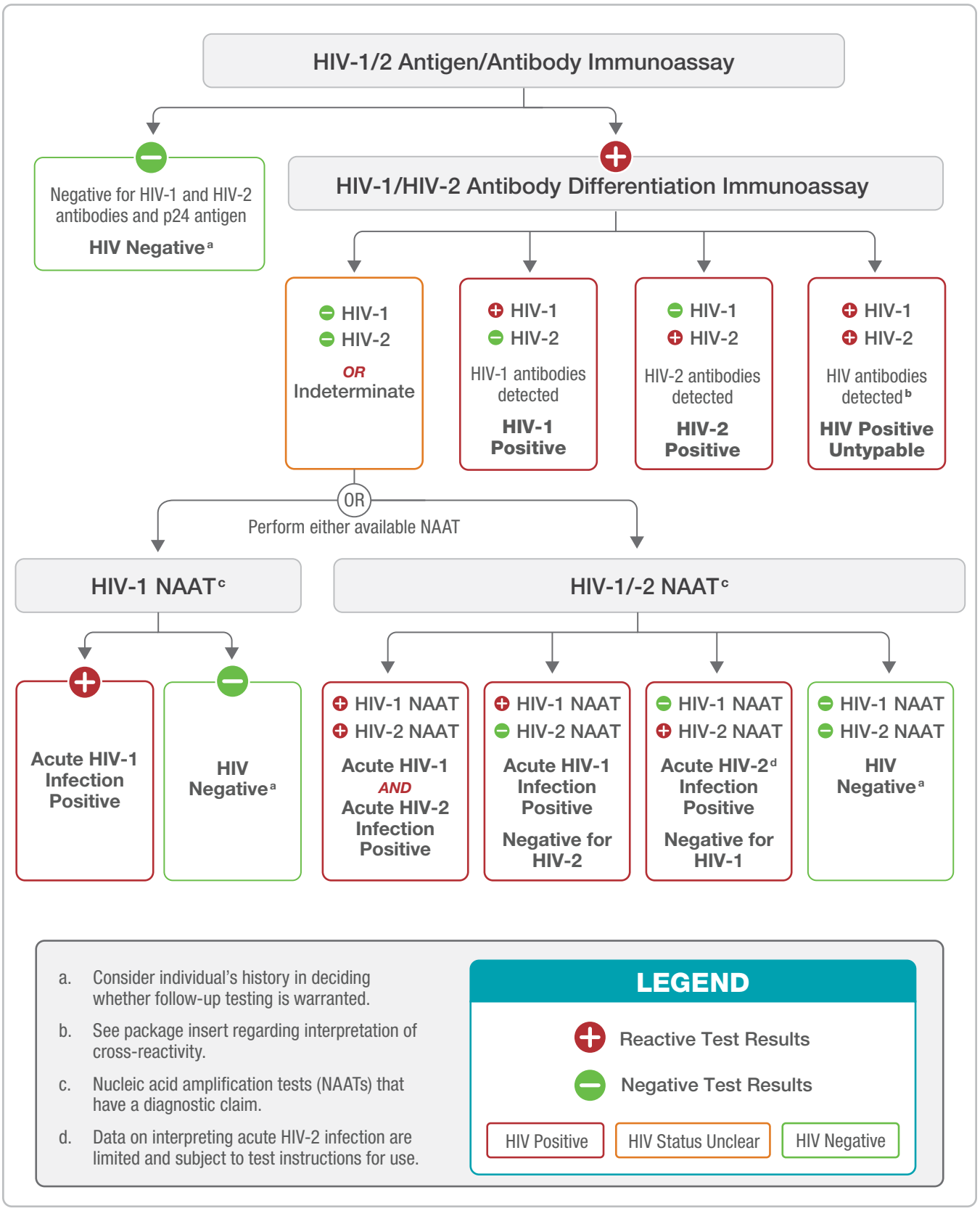
The HIV Laboratory Diagnostic Testing Algorithm[1] should be used for testing serum or plasma to diagnose persons with HIV and for the confirmation of rapid HIV test results, starting from Step 1 of the algorithm, also commonly referred to as the screening test. CDC maintains lists of FDA-approved assays that can be used for Step 1 (the HIV-1/2 Antigen/Antibody [Ag/Ab] Immunoassay).[19]

Step 1: The algorithm recommends initial testing with an HIV-1/2 antigen/antibody immunoassay (IA) which, if reactive, is followed by supplemental testing. Recent updates from CDC allow for the Determine™ HIV-1/2 Ag/Ab Rapid Test to be used in this first step for serum/plasma, though instrumented antigen/antibody immunoassays are preferred.[12]

Step 2: Specimens that are reactive in Step 1 will undergo supplemental testing in Step 2 with an HIV-1/HIV-2 antibody differentiation assay. The Geenius™ HIV-1/2 Supplemental Assay and the VioOne™ HIV Profile™ Supplemental Assay are both approved for this purpose.

Step 3: Specimens with a **Final Assay Interpretation** (Geenius) or a **Results Interpretation** (HIV Profile™) of HIV antibody negative or indeterminate by the HIV-1/HIV-2 antibody differentiation assay require further testing in Step 3. Specimens with HIV-2 antibodies detected, including those with a **Final Assay Interpretation** (Geenius) or a **Results Interpretation** (VioOne™ HIV Profile™) of HIV-2 Positive and HIV-2 Positive with HIV-1 cross reactivity, do not require further testing. Step 3 is the HIV-1 NAAT, of which three are described in this update. CDC maintains lists of FDA-approved assays for supplemental testing including HIV-1/HIV-2 antibody differentiation immunoassays and HIV-1 NAATs.[19] **Figure 6 (page 20)** provides an alternative visual representation of the HIV Laboratory Diagnostic Algorithm. It delineates the possible combinations of results from the algorithm and can be used in combination with **Table 1 (page 13)** to provide laboratory algorithm interpretations.

Figure 6: Laboratory Testing Algorithm in Serum/Plasma[k]



k Modified from 2014 algorithm figure and CDC Quick Reference Guide, available from: *Technical Update for HIV Nucleic Acid Tests Approved for Diagnostic Purposes*[5]

Figure 7: Laboratory Testing Algorithm, Utilizing HIV Differentiation NAAT as Second Step

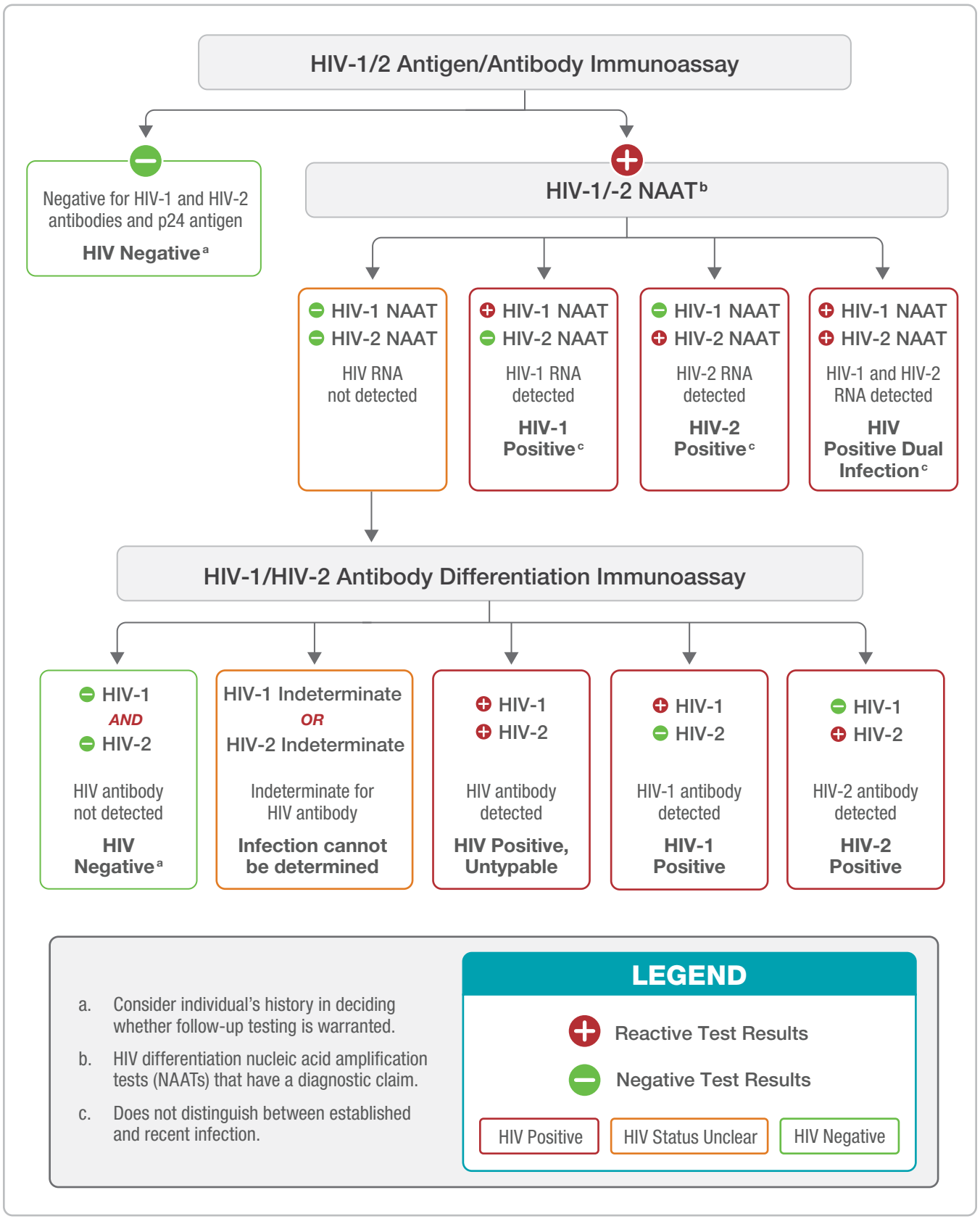
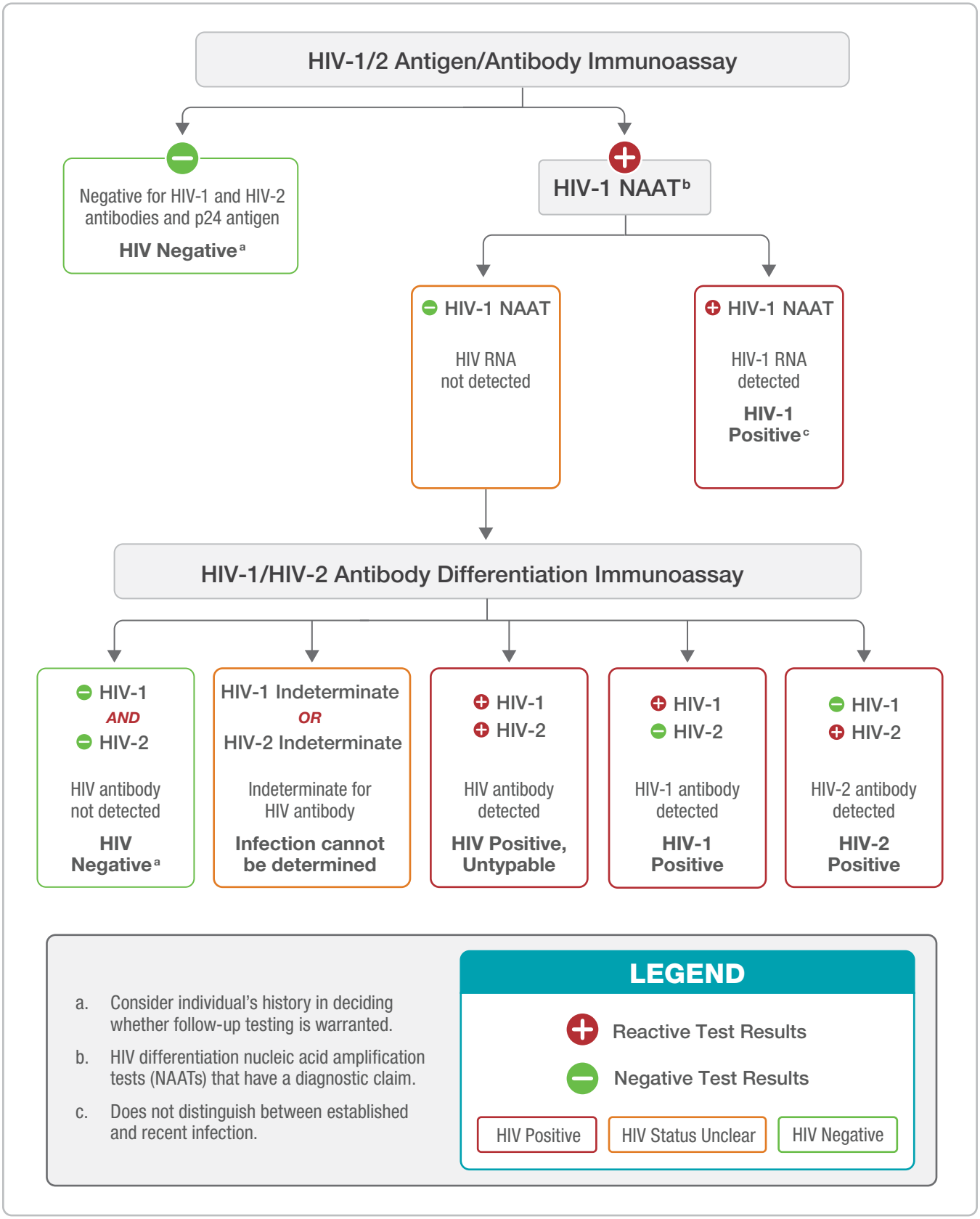


Figure 8: Laboratory Testing Algorithm, Utilizing HIV-1 NAAT as Second Step



Definitions

HIV-1/2 antigen/antibody immunoassay: This assay detects both HIV-1 and HIV-2 antibody and HIV-1 antigen. It is the recommended initial test in the HIV algorithm. The result from this test is either a simple reactive or nonreactive (Examples: Abbott Architect® HIV Ag/Ab Assay or Bio-Rad GS HIV Combo Ag/Ab) or may have more complex results (Example: Bio-Rad BioPlex® 2200 HIV Ag-Ab).

HIV-1/HIV-2 antibody differentiation immunoassay: This assay is able to distinguish between HIV-1 and HIV-2 antibodies and is intended for use as a supplemental assay. This assay is the recommended second step in the HIV testing algorithm following a reactive screening result. The results from this assay are called **Final Assay Interpretation**s and are included in the table in this document.

Assay Result: This is the term given to describe the result for a single assay or test in the HIV diagnostic algorithm. Some assays are capable of detecting or measuring multiple analytes. Laboratories should adhere to the format presented in the package insert for reporting the assay result.

Laboratory algorithm interpretation: This is the term used to describe whether a given specimen has laboratory evidence of an HIV infection. This is based on the combination of the assay results of each test in the HIV multi-test algorithm.

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