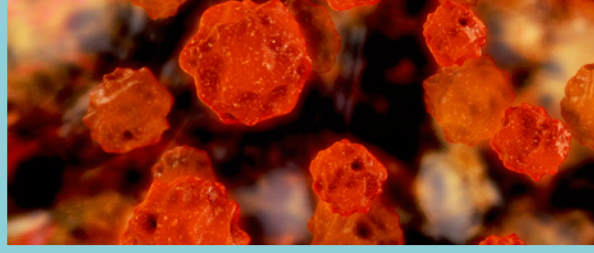
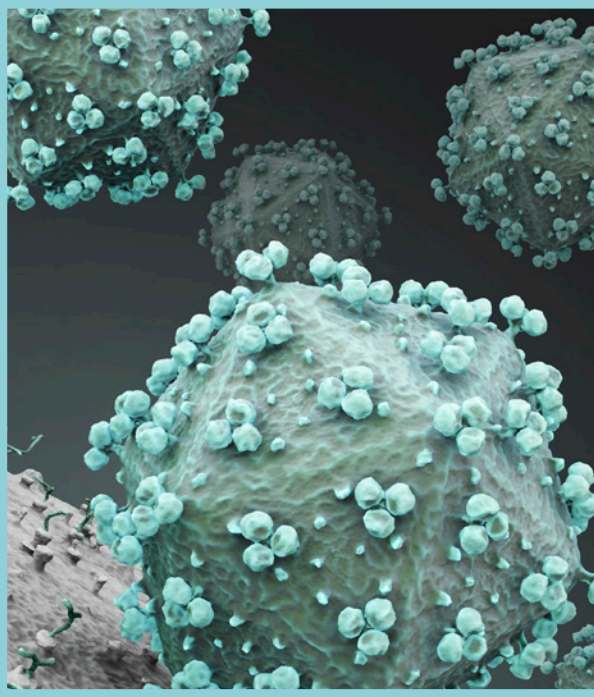
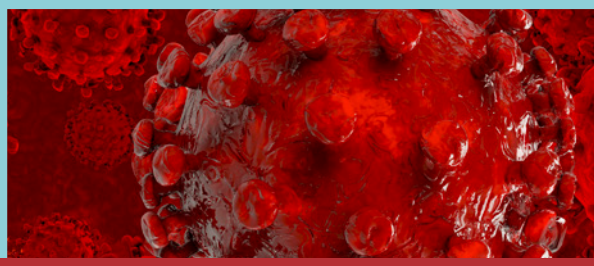
Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm







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APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES™

Introduction

To maximize public health impact, accurate, 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 final assay result of each test, and the final algorithm interpretation for the specimen.

Since the 2014 HIV Laboratory Testing Algorithm[1] (Appendix A, Figure 1) was released, several HIV diagnostic tests have been FDA-approved.[2] One such test is the Geenius™ HIV1/2 Supplemental Assay that produces results that were not generated by the previously available HIV-1/HIV-2 differentiation test, Multispot HIV-1/2. This document addresses the new final assay results that may be produced by the Geenius™ HIV1/2 Supplemental Assay and updates the corresponding final algorithm interpretation for laboratory reports. This document also serves as an overall update to the 2013 version, Suggested Reporting Language for the HIV Laboratory Diagnostic Testing Algorithm.[3] A second update is forthcoming to address changes introduced by the BioPlex 2200 HIV Ag-Ab assay. Information about the algorithm and definitions used throughout this document are addressed in Appendix A. Since the 2014 algorithm, several documents have been published that address the Geenius assay including an Informational Update from APHL,[2] a Technical Update from CDC,[4] and a Technical Bulletin by Bio-Rad.[5] This document incorporates aspects of the information from each of these documents to serve as a cohesive reference. The reporting language presented here is suggested for laboratories to use when reporting to healthcare providers and surveillance programs, but adjustments may be needed to meet individual facility or jurisdiction requirements. Major deviations should be considered carefully because misinterpretation of HIV test results can have serious implications.

Rationale for Document Update

Importance of Standardized Reporting Language

The use of standardized language when providing laboratory results is particularly important for testing that involves multi-test algorithms. The HIV Laboratory Testing Algorithm[1] (Appendix A, Figure 1) involves a series of tests, often performed by more than one laboratory, to determine the presence or absence of HIV infection. For more information about the algorithm and definitions used throughout this document please refer to Appendix A. Several HIV diagnostic tests that have been introduced to the market are designed to detect multiple analytes. The addition of multi-analyte tests to a multi-test algorithm makes interpreting results of the algorithm more complex 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 health care providers, unnecessary additional testing, delays in care for infected persons and inaccurate estimates of disease burden. In this document we have adopted the term "final assay result" to indicate the result from a specific assay, even if that assay detects multiple analytes. In the case of the Geenius HIV 1/2 Supplemental Assay, this final assay result is referred to as the "Assay Interpretation" in the package insert and/or the "Conclusion" on the printed report. We have also adopted the term "final algorithm interpretation" to represent the interpretation that should be

Final Assay Result: Term given to describe the result for a single assay or test in the HIV diagnostic algorithm. In cases where there are multiple analytes that the assay or test is able to measure it serves as the overall or summary result for the entire test. In the case of the Geenius HIV-1/2 Supplemental Assay the final assay result is referred to as the "Assay Interpretation" in the package insert and/or the "Conclusion" on the printed report.

Final Algorithm Interpretation: Term used to describe whether a given specimen has laboratory evidence of an HIV infection. This is based on the combination of the final assay result of each test in the HIV multi-test algorithm.

provided for the HIV multi-test algorithm. These terms are used throughout the document and within the accompanying table and are further defined in Appendix A. If the algorithm has not been completed for a specimen and the final algorithm interpretation cannot yet be determined, the laboratory report for that specimen should include which test results are pending and any additional tests that should be performed to establish the final algorithm interpretation. We strongly suggest that all laboratories that perform testing as part of the HIV Laboratory Testing Algorithm adopt the reporting language suggested in this document.

Considerations for Persons on Antiretroviral Therapy

One of the great achievements that has been made since the publication of our last reporting language document is the increase in the number of patients receiving 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.[6,7] Therefore, the final assay results and the final algorithm interpretation need to be considered in the context of the individual's clinical circumstances, including early ART. At this point, there is insufficient data regarding the performance of the algorithm and any potential effects of pre-exposure prophylaxis (PrEP).

Updates Due to Change in Supplemental Assay

In July 2016 the Multispot HIV-1/HIV-2 Rapid Test was discontinued, necessitating the transition to a new FDA-approved assay for HIV supplemental testing, the Geenius™ HIV 1/2 Supplemental Assay.[8] This assay introduced three new results (referred to as assay interpretations by the manufacturer) that were not generated by the Multispot. These new potential results, and other characteristics of the Geenius™ assay led to some confusion regarding reporting of the results. Documents from CDC[4] and Bio-Rad Laboratories[5] have been released to address the new results and clarify areas where confusion might occur. These two documents along with the following descriptions and table are intended to clarify complex testing outcomes and to guide laboratory reporting of test results to providers and health department surveillance programs.

Overall Comments on Reporting Geenius Results

The Geenius instrument automatically produces a printable test report at the completion of every test that includes both the assay interpretation, listed as the "Conclusion," and the individual HIV-1 and HIV-2 results in parenthetical notation.[5] While this file can be printed for recordkeeping purposes, most laboratories will use the information to create their own laboratory report.

In the case of the Geenius assay, the assay interpretation is considered the final assay result. When a laboratory is reporting results to healthcare providers and public health surveillance programs, the assay interpretation, referred to in this document as the final assay result, should always be included.

Reporting of the individual HIV-1 and HIV-2 results by the laboratory is not specifically prohibited by the manufacturer[8] but it is our recommendation that laboratories do not report this information. The performance characteristics of the Geenius assay that appear in the package insert are based on the assay interpretation and not the individual HIV-1 and HIV-2 results and 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, it is our recommendation 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.

We recommend that all laboratories include the final assay result on the laboratory report. We also recommend that laboratories exclude the individual HIV-1 and HIV-2 results from the Geenius Assay on the laboratory report.

Geenius Final Assay Results and Interpretations

Recommended Geenius final assay results and interpretations, with final algorithm interpretations and additional testing that is required are described below for results unique to the Geenius assay that are not addressed in the 2014 HIV Laboratory Testing Algorithm.[1] The Geenius package insert[8] includes a section on the interpretation of test results including a table (pg. 11) that displays both the HIV-1 and HIV-2 individual analyte results as well as the assay interpretation.

HIV-2 Positive with HIV-1 Cross Reactivity

This final assay result (assay interpretation) should be considered equivalent to the assay interpretation of "HIV-2 positive." The Geenius™ software has confirmed antibodies to HIV-2 but 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 assay interpretation is distinct from an "HIV Positive Untypable (undifferentiated)," which would indicate the possibility of a dual infection with HIV-1 and HIV-2.

Specimens with this final assay result (assay interpretation) do not require any additional testing. Persons with this final assay result should be provided appropriate counseling and linked to medical care.

HIV-2 Indeterminate

Specimens with this final assay result require additional testing. First, Geenius testing should be repeated with the same specimen on a new cartridge.

- If upon repeat testing the specimen's final assay result is "HIV-1 positive" or "HIV-2 positive," this should be reported as the final assay result for Geenius and no further testing is needed.
- If upon repeat testing the specimen's final assay result is "HIV-negative" this should be reported as the final result for Geenius and testing with an HIV-1 nucleic acid test (NAT) is indicated.
- If upon repeat testing the specimen's final assay result is "HIV-2 indeterminate," this should be reported as the final result for Geenius and an HIV-1 NAT should be conducted. Although the package insert[8] states that if a sample is repeatedly "HIV-2 indeterminate," testing should be repeated 2-4 weeks later with a new specimen, data presented subsequent to FDA approval at the 2016 HIV Diagnostics Conference,[9] indicate that some persons with a repeatedly "HIV-2 indeterminate" assay interpretation have acute HIV-1 infection.[4,10-12]
    - If HIV-1 RNA is detected, the final 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 different validated supplemental HIV-2 test (antibody test or NAT) if available. Alternatively, redraw and repeat the algorithm in 2-4 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 this final assay result should prompt the same testing sequence as described above for repeatedly reactive "HIV-2 indeterminate" final assay results. An HIV-1 NAT should be conducted:

- If HIV-1 RNA is detected the final algorithm interpretation would be: Positive for HIV-1, laboratory evidence of HIV-1 infection consistent with an acute or early 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 different validated supplemental HIV-2 test (antibody test or NAT) if available. Alternatively, redraw and repeat algorithm in 2-4 weeks to assess HIV-2 infection. Supplemental HIV-2 testing may be available through commercial laboratories, public health laboratories or CDC.

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

Test Sequence			Final Algorithm Interpretation[d]	Interpretation for Provider[e] (Sample should be reported as:)	Further Actions[f]
Step 1	Step 2	Step 3			
HIV-1/HIV-2 Ag/Ab IA[b]	HIV-1/HIV-2 Antibody Differentiation IA[c]	HIV-1 NAT			
Nonreactive	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 NAT or request a new specimen and repeat the algorithm according to CDC guidance.[g]
Reactive	HIV-1 Positive	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.[h]
Reactive	HIV-2 Positive	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.[h]
Reactive	HIV-2 Positive with HIV-1 Cross reactivity	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 (undifferentiated).	Link patient to HIV medical care and provide appropriate prevention counseling.[h]
Reactive	HIV Positive untypable (undifferentiated)	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.[h] 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, HIV-2 indeterminate,[i] HIV indeterminate	Detected	Positive for HIV-1. Laboratory evidence of HIV-1 infection consistent with an **acute** HIV-1 infection.	**Acute** HIV-1 Positive	Link patient to HIV medical care and provide appropriate prevention counseling[h] immediately to expedite prevention practices.
Reactive	HIV-1 indeterminate	Not detected	HIV-1 antibodies were not confirmed and HIV-1 RNA is not detected.	HIV Negative	If recent HIV exposure is suspected or reported, conduct HIV-1 NAT or request a new specimen and repeat the algorithm according to CDC guidance.[g]
Reactive	HIV-2 indeterminate[i]	Not detected	HIV antibodies were not confirmed and HIV-1 RNA is not detected.	HIV-1 Negative, HIV-2 Inconclusive	Refer sample for testing with a different validated supplemental HIV-2 test (antibody test or NAT) if available. Alternatively, redraw and repeat algorithm in 2-4 weeks to assess HIV-2 infection.
Reactive	HIV Indeterminate	Not detected	HIV-1 antibodies were not confirmed and HIV-1 RNA is not detected.	HIV-1 Negative, HIV-2 Inconclusive	Refer sample for testing with a different validated supplemental HIV-2 test (antibody test or NAT) if available. Alternatively, redraw and repeat algorithm in 2-4 weeks to assess HIV-2 infection.
Reactive	Negative	Detected	Positive for HIV-1. Laboratory evidence of HIV-1 infection consistent with an **acute** HIV-1 infection.	**Acute** HIV-1 Positive	Link patient to HIV medical care and provide appropriate prevention counseling immediately to expedite prevention practices.[h]
Reactive	Negative	Not detected	HIV-1 antibodies were not confirmed and HIV-1 RNA is not detected.	HIV-1 Negative	If recent HIV exposure is suspected or reported, conduct HIV-1 NAT or request a new specimen and repeat the algorithm according to CDC guidance.[g]
Reactive	Negative or indeterminate	Invalid or not performed	Inconclusive	Inconclusive	Request an additional specimen and repeat the algorithm. Ensure HIV-1 NAT is performed if indicated by results of HIV-1/HIV-2 Ag/Ab IA and HIV-1/HIV-2 Ab differentiation IA.

a. The tests outlined in this table are not suitable for oral fluid or dried blood spots. **b.** The need for repeating screening IA on an initial reactive test is assay dependent; refer to product package insert. **c.** This column contains the final assay interpretation per the Geenius package insert, the only FDA approved test for this step. We recommend excluding the individual HIV-1 and HIV-2 results on the laboratory report. If they are used, the final assay interpretation or final assay result should also be included. **d.** This column contains suggested language to be used for the laboratory report and it can be directly used for reporting from LIMS systems. **e.** This column contains simplified language of the previous column, "Final 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. **f.** 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. **g.** Please refer to the Centers for Disease Control and Prevention Laboratory Guidance. Available at https://www.cdc.gov/hiv/testing/laboratorytests.html **h.** Please refer to the Centers for Disease Control and Prevention HIV Guidelines and Recommendations to find the most appropriate information by age and risk group for the patient in question. Available at https://www.cdc.gov/hiv/guidelines/index.html **i.** Follow Geenius package insert and refer to the CDC Technical Update. Available at https://stacks.cdc.gov/view/cdc/40790

Guidance on Reporting Test Results to Health Care Providers

All laboratory reports should include the final assay result for all tests performed as well as a final algorithm interpretation of the HIV Laboratory Testing Algorithm that is generated from the combination of final assay results. Health care providers may be receiving results from one or multiple laboratories. If the laboratory reporting the results to the provider did not conduct all of the testing, they may not have access to other results and may not be able to provide a final algorithm interpretation.

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 antiretroviral treatment (ART), for the purpose of verifying 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.[7] In such cases, serological tests may be nonreactive or indeterminate and HIV RNA may be undetectable due to ART, leading to a false negative outcome. 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 is recommended.

The table includes a column, "Interpretation for Provider" which is a simplified version of the final algorithm interpretation. The information in this column is included as a resource for providers and public health surveillance programs that may use this document and does not need to be included on the laboratory report. Additionally, the further actions included in the table are also provided to help guide submitters on appropriate next steps following testing.

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

1. Laboratories should specify the assays that were used in HIV testing (See Appendix A for links to lists of FDA-approved tests) and the final assay results for each assay.
2. If laboratories use an alternative testing sequence (i.e. a testing sequence other than the 2014 recommendations) or alternative assays (i.e. an assay sequence other than the 2014 recommendations), reports should describe the limitations associated with the testing sequence used. Refer to Laboratory Testing for the Diagnosis HIV Infection: Updated Recommendations for more information on the limitations associated with alternatives to the recommended algorithm.[1]
3. Laboratories may issue preliminary reports containing the final assay 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, any additional tests that are necessary to establish the final algorithm interpretation and recommend any additional testing that may be required. The final report should contain the final algorithm interpretation.
4. Health care providers may be receiving results from one or multiple laboratories. Each laboratory should be reporting the final assay result from the tests performed. Additionally, where possible and applicable the laboratory report should also include a final algorithm interpretation and recommendations for appropriate further actions. If the laboratory reporting the results to the provider did not conduct all of the testing, they may not have access to other results and may not be able to provide a final algorithm interpretation.
5. The diagnosis of acute HIV infection has implications for increased risk of transmission to uninfected partners and potential public health interventions. Laboratories should have arrangements in place to expedite reporting of test results indicative of acute HIV infection to the health care provider and to the health department.

Guidance on Laboratory Reporting for Surveillance

All states, the District of Columbia, and United States 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.[15] Requirements of state or local health departments might differ; therefore, follow the requirements of your jurisdiction.

All laboratory reports should include the final assay result for all tests performed as well as a final algorithm interpretation of the HIV Laboratory Testing Algorithm that is generated from the combination of final assay results. Health Department surveillance programs may be receiving results from one or multiple laboratories. If the laboratory reporting the results did not conduct all of the testing, they may not have access to other results and may not be able to provide a final algorithm interpretation. Therefore, the burden of combining these results may fall to the surveillance program. This reporting language document and table can be used as a resource to understand the results from multiple laboratories.

Electronic Lab Reporting (ELR) Guides for HIV Surveillance

Electronic Lab Reporting (ELR) Guides are available from the HIV Surveillance program in your state or the CDC that summarize information obtained from health departments, manufacturers, commercial laboratories, ELR coordinators, APHL and other organizations regarding various HIV assays. Each guide provides information that will help public health ELR coordinators determine how to parse the results transmitted in an HL7 2.3.1 or 2.5.1 message. This document will provide information regarding the LOINC and SNOMED codes that may be used. Additionally, this document provides HIV surveillance programs information regarding the various ways the results can be reported as well as guidance regarding how to capture the results in the eHARS HIV surveillance registry.

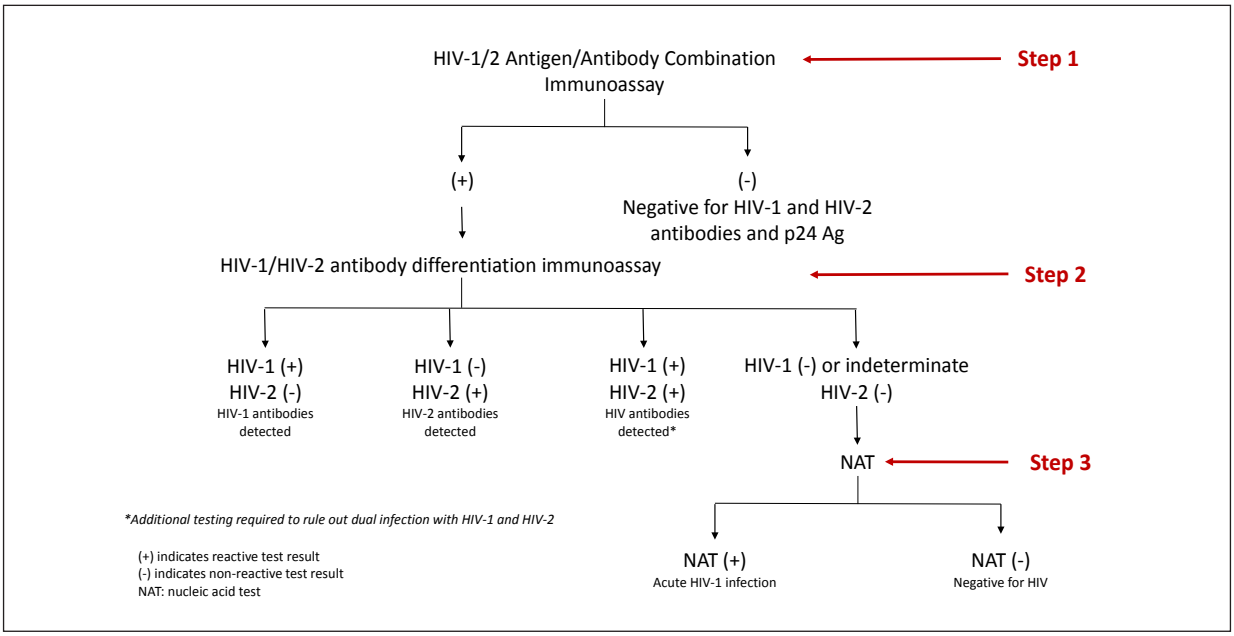
The table includes a column, "Interpretation for Provider" which is a simplified version of the final algorithm interpretation. The information in this column is included as a resource for providers and public health surveillance programs that may use this document and does not need to be included on the laboratory report. Additionally, the further actions included in the table are also provided to help 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 maintains a listing and provides contact information for state HIV surveillance coordinators available at https://www.nastad.org/membership-directory.

Appendix A

The HIV Laboratory Diagnostic Testing Algorithm[1] (Figure 1) is a sequence of multiple tests in which the final algorithm interpretation relies on the final assay results from one or more tests. The algorithm 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. The algorithm recommends initial testing with an HIV-1/2 antigen/antibody combination immunoassay (IA) which, if reactive, is followed by supplemental testing or Step 2 in the diagram below with an HIV-1/HIV-2 antibody differentiation assay. The only assay currently FDA-approved and manufactured is the Geenius™ HIV-1/2 Supplemental Assay. Specimens negative or indeterminate by the HIV-1/HIV-2 antibody differentiation assay require further testing by an HIV-1 nucleic acid test (NAT) which is considered step 3 in the figure below. CDC maintains lists of FDA approved assays that can be used for Step 1 (the HIV-1/2 Antigen/Antibody Combination Immunoassay[16]) and for Step 2 and 3 (supplemental testing including HIV-1/HIV-2 antibody differentiation immunoassay and HIV-1 NATs).[17]

Figure 1: HIV Laboratory Diagnostic Testing Algorithm (adapted from CDC and APHL-Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. 2014[1])



HIV-1/2 antigen/antibody combination immunoassay (IA): These assays detect both HIV-1 and HIV-2 antibody and HIV-1 antigen. It is the recommended initial test in the HIV algorithm. The final assay result from this test is either reactive or nonreactive. (Examples: Abbott Architect HIV Ag/Ab Combo Assay, Advia Centaur HIV Ag/Ab Combo, Bio-Rad GS HIV Combo Ag/Ab EIA, 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. This assay is the recommended second step in the HIV testing algorithm following a reactive screening result. The test has multiple final assay results (Table 1). (Example: Bio-Rad Geenius HIV 1/2 Supplemental Assay)

Final Assay Result: Term given to describe the result for a single assay or test in the HIV diagnostic algorithm. In cases where there are multiple analytes that the assay or test is able to measure it serves as the overall or summary result for the entire test. In the case of the Geenius HIV-1/2 Supplemental Assay the final assay result is referred to as the "Assay Interpretation" in the package insert and/or the "Conclusion" on the printed report.

Final Algorithm Interpretation: Term used to describe whether a given specimen has laboratory evidence of an HIV infection. This is based on the combination of the final assay result of each test in the HIV multi-test algorithm.

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