CENTERS FOR DISEASE CONTROL AND PREVENTION

Technical Update on HIV-1/2 Differentiation Assays

In response to changes in the commercial availability of HIV-1/HIV-2 antibody differentiation assays approved by the U.S. Food and Drug Administration (FDA) for diagnostic use, the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) are writing to share information on the only available differentiation assay as well as interim solutions for HIV testing.

The CDC and APHL continue to recommend that laboratories use a laboratory-based HIV antigen/antibody HIV screening immunoassay, followed, when reactive, by an HIV-1/HIV-2 antibody differentiation immunoassay. When the differentiation assay returns a negative or indeterminate result, perform an HIV-1 nucleic acid test (NAT).[1] In addition to being accurate, HIV testing should be expedited to reduce the time to antiretroviral treatment because infected persons have better health outcomes when they are treated earlier and treatment of infected persons reduces transmission of HIV to others.

Results provided by new HIV-1/HIV-2 antibody differentiation supplemental assay

There is one FDA-approved HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing that continues to be manufactured (Geenius™ HIV 1/2 Supplemental Assay, Redmond, WA). Its package insert provides test result reporting language that should be followed. The test produces three results not generated by its predecessor: HIV-2 positive with HIV-1 cross reactivity, HIV-2 indeterminate, and HIV indeterminate.[2]

- An HIV-2 positive with HIV-1 cross reactivity result should be considered HIV-2 positive. This result is distinct from HIV positive untypable (undifferentiated), which would indicate the possibility of dual infection with HIV-1 and HIV-2. Persons with either result should be referred to medical care.
- Specimens with HIV-2 indeterminate results require additional testing. First, Geenius testing should be repeated with the same specimen. If the specimen tests HIV-negative on repeat this should be reported as the final result for the Geenius and testing with an HIV-1 NAT is indicated. If the specimen is repeatedly HIV-2 indeterminate, then according to the package insert,[3] testing should be repeated 2-4

- weeks later with a new specimen. However, data presented at the 2016 HIV Diagnostics Conference that became available after FDA approved the package insert indicate that some persons with repeatedly HIV-2 indeterminate results have acute HIV-1 infectiion.[4-6] If a specimen repeatedly produces HIV-2 indeterminate results, an HIV-1 NAT should be conducted. If HIV-1 RNA is detected by NAT, this result indicates acute HIV-1 infection, and the person should be referred for immediate medical care. If the HIV-1 NAT result is negative, refer the specimen for testing with a different validated supplemental HIV-2 test (antibody test or NAT) or repeat testing in 2 to 4 weeks. Supplemental HIV-2 testing may be available through commercial laboratories, public health laboratories or CDC.

- HIV indeterminate results should prompt the same testing sequence as described above for repeatedly HIV-2 indeterminate results. First, an HIV-1 NAT should be conducted. If HIV-1 RNA is detected by NAT, this result indicates acute HIV-1 infection, and the person should be referred for immediate medical care. If the HIV-1 NAT result is negative, refer the specimen for testing with a different validated supplemental HIV-2 test (antibody test or NAT) or repeat testing in 2 to 4 weeks. Supplemental HIV-2 testing may be available through commercial laboratories, public health laboratories or CDC.

There may be circumstances under which a laboratory is unable to adopt the FDA-approved HIV-1/HIV-2 antibody differentiation immunoassay. In this situation, a laboratory has alternatives for that step in the algorithm, some of which could delay turnaround time for test results.

- Send specimens to another laboratory that offers the FDA-approved supplemental HIV antibody differentiation assay.
- Refer to CDC/APHL laboratory testing guidance section I, “Alternative Testing Sequences When Tests in the Recommended Algorithm Cannot be Used” [pages 19-20].[1]

- Validate another HIV test for use as a supplemental antibody test. A validated test is one for which an individual laboratory has demonstrated the ability to produce accurate results according to the standards of the Clinical Laboratory Improvement Amendments (CLIA) or other regulatory entities and can therefore be used to report clinical results for diagnosis and patient management.

There will remain cases for which diagnostic tests and algorithms are not accurate. Biologic causes for false-positive and false-negative HIV test results have been reported. Pre- and post-analytic steps such as incorrect specimen type, specimen mix-up, mislabeling or data transcription errors can also lead to incorrect HIV test results. Inconsistent or conflicting test results should therefore be investigated with follow-up testing on a newly collected specimen.

Thank you for your commitment to accurate laboratory testing for HIV. Please send any comments or questions to www.cdc.gov/info or 1-800-CDC-INFO.

1. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. 2014. http://stacks.cdc.gov/view/cdc/23447. Accessed June 27, 2016.
2. Association of Public Health Laboratories. HIV Diagnostic Informational Updates. 2016. http://www.aphl.org/programs/infectious_disease/Documents/2015_Informational%20Update_02_12_16_FINAL.pdf.
3. Bio-Rad Laboratories. Geenius HIV 1/2 Supplemental Assay. 2014; http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM420735.pdf.
4. Delaney KP, Ethridge SF, Adams S, et al. Evaluation of Newly Approved HIV Antigen-Antibody Tests Individually and When Used in the CDC/APHL HIV Diagnostic Algorithm *HIV Diagnostics Conference.* 2016. https://custom.cvent.com/BEED90636AE44DD0A76741F3CCF3692C/files/650b3c4a6987431e9a96e36ddacac677.pdf. Accessed 07/25/2016.
5. Luo W, Adams S, Sullivan V, et al. Performance Evaluation of HIV Supplemental Assays. *HIV Diagnostics Conference.* 2016. https://custom.cvent.com/BEED90636AE44DD0A76741F3CCF3692C/files/76e45b22bb6841e4bf2f822af4fdcd41.pdf. Accessed 07/26/2016.
6. Bennett SB, Fordan S, Crowe S, et al. Comparative Performance of the Geenius HIV-1/HIV-2 Supplemental Test in Florida's Public Health Testing Population. *HIV Diagnostics Conference.* 2016. https://custom.cvent.com/BEED90636AE44DD0A76741F3CCF3692C/files/8d8b37174d9d4d2d8790cba0131ceeec.pdf.