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Highlights from the 2016 HIV diagnostics conference: The new landscape of HIV testing in laboratories, public health programs and clinical practice

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Abstract

The 2016 HIV Diagnostics Conference, held in Atlanta, Georgia, was attended by public health officials, laboratorians, HIV testing program managers, surveillance coordinators and industry representatives. The conference addressed test performance data, the implementation of new testing algorithms, quality assurance, and the application of new tests in a variety of settings. With regard to the recommended Centers for Disease Control and Prevention/Association of Public Health Laboratories HIV laboratory testing algorithm, the conference featured performance data, implementation challenges such as a lack of test options for the second and third steps, as well as data needs for new tests that may be used as part of the algorithm. There are delays when nucleic acid testing is needed with the algorithm. Novel tests such as point of care nucleic acid tests are needed on the U.S. market to readily identify acute infection. Multiplex tests are being developed which allow for the simultaneous detection of multiple pathogens. CDC staff highlighted new guidance for testing in non-clinical settings. Innovative approaches to linking testing and care in some settings have led to identification of early infections, improved receipt of test results and expedited initiation of therapy. Work continues to optimize testing so that infections are accurately identified as early as possible and time to treatment is minimized to improve health outcomes and prevent transmission.

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None declared.

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1. Introduction

The 2016 HIV Diagnostics Conference, which occurred March 21–24, 2016, in Atlanta, Georgia, was convened by the Centers for Disease Control and Prevention (CDC), the Association of Public Health Laboratories (APHL), the American Sexual Health Association and the American Sexually Transmitted Diseases Association. It was attended by public health officials, laboratorians, HIV testing program managers, surveillance coordinators and industry representatives. This unique confluence of subject matter experts involved in every aspect of HIV testing fosters the development and use of new HIV testing technology in the United States. The conference offers a unique opportunity for persons involved in HIV testing to become familiar with test performance data, the implementation of new testing algorithms, quality assurance, and the application of new tests in a variety of settings. Testing is the gateway to treatment, so, fittingly, attendees emphasized the need to use accurate diagnostic tests and to decrease time to treatment for infected persons to improve health outcomes and prevent infections [1]. This report describes highlights of the conference from the perspectives of co-authors who participated.

Opening night presentations addressed diagnostic terminology and performance measures. There is movement toward describing the analytes an assay detects and away from using “generation” terms (e.g., antigen/antibody immunoassay instead of fourth-generation assay) [2]. There was a discussion on how to evaluate HIV test performance that included the impact on specificity of maximizing sensitivity [3]. If the penalty for missing a case is high (i.e., the disease is fatal, treatment exists or it spreads easily), a test cut-off should be set to maximize true positives, which may increase the number of false positives. When prevalence is low, positive screening test results are often false positive (i.e., low positive predictive value). Further, methods to calculate algorithm performance were discussed. Food and Drug Administration (FDA) staff provided an overview of HIV test regulations and the components of a package insert [4].

2. HIV laboratory testing algorithm

The 2014 laboratory testing algorithm recommended by CDC and APHL was designed to improve the detection of acute HIV-1 infections, reduce the time to testing completion, and accurately diagnose HIV-2 [5]. An APHL survey indicates that 55% of public health laboratories used the algorithm in 2014 [6]. The algorithm performed as expected. Early infection detection is similar for different laboratory-based antigen/antibody tests, and is better than for IgM-sensitive tests [7]. The likelihood of detecting acute infections depends on the population undergoing testing and the frequency of testing. A large metropolitan medical system demonstrated the algorithm’s ability to detect acute infections [8]. Data on the algorithm’s impact on turnaround time and testing costs can be found in two papers in this issue: “Real-world Performance of the New US HIV Testing Algorithm in Medical

Settings" and "Comparison of Turn-Around Time and Total Cost of HIV Testing Before and After Implementation of the 2014 CDC/APHL Laboratory Testing Algorithm for Diagnosis of HIV Infection".

A roundtable session addressed algorithm implementation issues [9]. Some attendees expressed interest in using the Determine HIV–1/2 Ag/Ab Combo (Orgenics Ltd., Israel, Determine) rapid test instead of a laboratory based antigen/antibody test as the initial test in the algorithm. Laboratorians from low prevalence states described sharing supplemental antibody testing by conducting it at a central laboratory, a strategy which may decrease cost but likely increases turnaround time relative to testing in the original laboratory. Others wanted to proceed directly to nucleic acid tests (NAT) after a reactive screening test, and to conduct supplemental antibody tests only when the NAT is negative. Considering the currently available NATs, this may increase cost, including up-front costs associated with validation if the laboratory chooses to use a viral load test.

3. Nucleic acid testing

The laboratory testing algorithm provides timely results for antibody positive specimens, particularly when supplemental testing is conducted in the same laboratory [10]. However, delays may occur when nucleic acid testing is needed. Many laboratories do not perform NATs because they are expensive, technically challenging, or needed too infrequently. To compound the issue, only one NAT, a qualitative HIV-1 RNA assay, is approved for diagnostic use in the United States. If a laboratory uses a viral load test as the NAT in the algorithm, it must be ordered by a physician unless the laboratory has conducted an appropriate validation study to modify use of the test for diagnosing HIV-1 infection. Specimens used to initiate the laboratory algorithm may have insufficient volume or be inappropriate for NAT, so retrieval of a follow-up specimen may be necessary. This is problematic because clinicians should rapidly distinguish acute infections from antigen/antibody immunoassay false positive tests [8].

Conference participants inquired whether manufacturers of HIV viral load tests will seek an FDA claim to change the intended use statement of the tests to include diagnosis as has occurred for at least one hepatitis C viral load test. They also asked whether an HIV viral load test used for diagnostic purposes would be a lab developed test (LDT) as updated LDT guidance has not been finalized by FDA. Over thirty public health laboratories use a shared services model to obtain NAT as part of the laboratory algorithm, though the time from specimen collection to NAT results is approximately 10 days, which does not include the provision of results to the individual tested [11]. Accessible, less costly NATs are needed so that test result provision and linkage to care and partner services can be expedited.

Alternative quantitative and qualitative options for simplified NAT are on the horizon, but the timeline for their availability on the U.S. market is unclear [2]. Conference attendees expressed concern that like antigen/antibody tests that entered the U.S. market years after other countries, there will be a considerable delay in the availability of simplified NAT due to regulatory hurdles the manufacturers will have to overcome [12]. This prompted a discussion on the appropriate pathway to engage and collaborate with FDA to ease

regulatory requirements so that tests such as these, which are necessary for identifying acute infections and monitoring viral suppression expeditiously, can enter the U.S. market as soon as possible.

4. Impact of three new tests on the laboratory algorithm

Two screening tests (Determine, and BioPlex 2200 HIV Ag-Ab assay (Bio-Rad Laboratories, Hercules, CA, BioPlex)) and one supplemental antibody test (Geenius HIV-1/2 Supplemental Assay, Bio-Rad Laboratories, Redmond, WA, Geenius) which were recently FDA approved may impact the laboratory algorithm [13]. The Determine rapid test provides separate results for HIV-1 p24 antigen and HIV-1/2 antibody. It detects infection earlier than IgM/IgG sensitive assays when used with plasma, but after antigen/antibody laboratory assays that use larger sample volume and have more complex technology [14]. Its use is not currently recommended in the laboratory algorithm. In order for CDC/APHL to make recommendations for the use of Determine in laboratory settings, published data are needed on the performance of (1) Determine with serum, plasma and whole blood when it is used as the initial test in the algorithm and (2) antibody supplemental test and HIV-1 nucleic acid test results when the p24 antigen component of the test is reactive. Some attendees indicated that Determine may be useful as a screening test in the laboratory algorithm in small volume laboratories, and in clinical laboratories needing immediate results. In a conference follow-up survey, approximately one-third of respondents indicated that they would use Determine with plasma in the laboratory algorithm if it were given as an alternative.

BioPlex, a multiplex bead immunoassay, gives separate results for HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen. It detects early infection at approximately the same time as other laboratory antigen/antibody tests and is highly sensitive for established infections [7]. Published data are needed on (1) its performance in combination with Geenius and HIV-1 NAT (2) the results of HIV-1 NAT and HIV-2 NAT testing if Bioplex is HIV-2 Ab reactive and Geenius is not HIV-2 positive (3) the results of supplemental antibody testing and HIV-1 nucleic acid testing after BioPlex results where only HIV-1 p24 antigen is reactive.

Geenius is the only FDA approved supplemental HIV-1/HIV-2 differentiation test remaining on the market. An article in this issue, “Comparative Performance of the Geenius HIV-1/HIV-2 Supplemental Test in Florida’s Public Health Testing Population”, reports on its performance in an evaluation at the Florida Bureau of Public Health Laboratories. In a study using stored serum/plasma specimens from a high risk population, 99.8% of HIV-1 Western blot positive specimens were detected by Geenius and there were no false positive algorithm results (i.e., reactive antigen/antibody assay and Geenius results in an uninfected specimen) [7]. Geenius sensitivity and specificity was similar to that of the previous differentiation test on the market, Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories, Redmond, WA, Multispot) [7]. Specimens that were HIV-2 positive using Multispot generated a variety of Geenius results: HIV-2 positive, HIV-2 positive with HIV-1 cross reactivity, HIV untypable, HIV-2 indeterminate and HIV negative [15]. The test generates three results that Multispot did not: HIV-2 positive with HIV-1 cross reactivity, HIV-2 indeterminate, and HIV indeterminate. Specimens with results that are HIV-2 positive with HIV-1 cross reactivity

should be considered HIV-2 positive for reporting. HIV-2 indeterminate test results for samples from persons without HIV-2 risk factors should be confirmed by retesting with Geenius using a new cassette [16]. An HIV indeterminate result occurs in specimens with bands to both HIV-1 and HIV-2 detected that do not meet the criteria for HIV-1 positive or HIV-2 positive.

Several instances of repeat HIV-2 indeterminate results were reported during the conference. They were reported for specimens from persons with acute HIV-1 infection, false positive antigen/antibody or IgM/IgG immunoassay results, and HIV-2 infected specimens [7,15,17]. The gp36 band was only detected in HIV-2 indeterminate results arising from true HIV-2 infections, while gp140 was the only band present for the HIV-2 indeterminate results from specimens with false positive antigen/antibody results. One solution to improve accuracy would be for the manufacturer to alter the internal proprietary algorithm used for defining HIV-2 reactivity.

Published data are needed on Geenius performance and cost as well as this algorithm pathway: following a reactive laboratory antigen/antibody assay result, if a specimen repeatedly produces HIV-2 indeterminate results or HIV indeterminate results, conduct an HIV-1 NAT because some specimens with these results are acutely infected with HIV-1. If HIV-1 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 is negative, conduct a validated supplemental HIV-2 test or repeat testing in 2–4 weeks. There are no HIV-2 nucleic acid tests approved by the FDA for diagnosis. Two presentations addressed the performance of new laboratory developed HIV-2 NATs, one on the detection and quantification of HIV-2 proviral DNA using droplet digital PCR and another on an HIV-2 total nucleic acid qualitative assay using the Abbott m2000 platform [18,19].

5. Alternatives to the recommended laboratory algorithm

Two studies examined the signal to cut-off ratio for the ARCHITECT HIV Ag/Ab Combo (Abbott Laboratories, Abbott Park, IL, ARCHITECT). The first provided data on repeating the ARCHITECT in duplicate only when the initial run had a signal to cut-off ratio of less than 10 rather than on all initially reactive samples in order to improve turnaround time and decrease cost [20]. This approach is not FDA-approved, so validation is required. The second indicated that a high signal to cut-off ratio predicted HIV infection but a low ratio does not rule-out acute HIV infection, and requires nucleic acid testing for resolution [8]. In a third study, the U.S. Army used a separate antigen/antibody assay after a reactive antigen/antibody assay in its HIV Diagnostic Algorithm to improve the positive predictive value of the initial result and decrease the amount of supplemental testing needed [21].

6. Surveillance

HIV testing data are used by surveillance units to describe disease burden, monitor progress toward prevention goals, and identify HIV-diagnosed individuals who are not in care so that they can be linked with a provider [22,23]. Challenges to obtaining accurate, complete data include incomplete reporting of all tests performed for an individual, health care provider

confusion with ordering tests and health department/provider confusion with laboratory report interpretation. The surveillance issues associated with implementation of the laboratory testing algorithm were the topic of a roundtable discussion led by staff from four state health departments [24]. The roundtable brought additional hurdles to light such as the lack of awareness by some laboratories that negative supplemental antibody tests should be followed with a nucleic acid test, inconsistent use of LOINCs (Logical Observation Identifiers Names and Codes) or the use of proprietary coding by reporting laboratories, the frequent need to link results from multiple testing laboratories for a given specimen to reach a final algorithm result, and the fact that many cases do not represent newly diagnosed persons. The need to educate laboratorians and clinicians on the laboratory testing algorithm emerged repeatedly. New York Department of Health staff presented on a web-based toolkit and webcast they created to assist laboratory directors with overcoming potential barriers to implementing the algorithm [25]. This approach combined web-based access to resources on testing recommendations, regulations, reporting guidelines and reimbursement along with practical information from laboratorians who had implemented the algorithm.

7. CLIA-waived testing

A conference session was dedicated to testing that occurs outside of traditional laboratory settings with CLIA-waived rapid tests. CDC staff presented 2016 non-clinical testing guidance which features practical considerations for HIV testing providers and gives information on programmatic issues and updates that impact HIV testing service delivery. It complements “Planning and Implementing HIV Testing and Linkage Programs in Non-clinical Settings”, which includes the benefits and drawbacks for different testing algorithms that can be used in non-clinical settings, a topic of interest at the conference. Conference attendees discussed whether a person with a single positive rapid test should be referred to care, and the consensus was that it depends on community prevalence. Testing guidance documents can be found along with other HIV testing resources at www.cdc.gov/hiv/testing/.

A consultant from National Alliance of State and Territorial AIDS Directors (NASTAD) described key points from their 2015 survey of health department HIV testing programs [26]. The survey indicated that oral fluid testing has decreased substantially since 2009. In addition, only a third of respondents conduct third-party billing for health department delivered HIV testing services. Finally, most health departments do not plan to support self-testing activities.

Citing their self-testing study, CDC authors pointed out that without in-person training, the majority of internet-recruited men who have sex with men who reported their results online successfully conducted rapid testing on themselves and collected dried blood spots [27]. Self-testing may allow persons who would not otherwise test to do so, though methods for successful linkage of persons with HIV infection must be examined.

A new CDC study conducted by the University of Washing-ton, Diagnostic Evaluation To Expand Critical Testing Technologies (DETECT), will assess the performance of new rapid tests, evaluate seroconversion sensitivity via serial follow-up with whole blood, oral fluid

and plasma and examine risk characteristics of those identified in seroconversion [28]. Also, evidence was presented that when the INSTI HIV-1/HIV-2 Rapid Antibody test (bioLytical Laboratories Inc., Richmond, BC, Canada) is used with simulated whole blood, it performs similarly to plasma for detection of early HIV-1 infection [29].

8. Linkage to care

In addition to test performance, there were presentations on the real-world application of testing and its impact on linkage to HIV care. When using the laboratory algorithm, some persons may not get their results or results may be delayed. Part of the impetus for beginning a statewide rapid testing algorithm program in New Jersey was the fact that 25% of persons did not receive their Western blot test results after a reactive rapid test [30]. After expanding the program, most people screened by a rapid test receive verification and linkage within 2 business days. The testing program has reduced the time to linkage through the use of local linkage to care collaboratives and 74% of clients are linked to HIV care within 30 days. It embeds HIV Prevention Patient Navigators in large HIV clinics to initiate, monitor and follow-up with newly engaged clients.

A roundtable session was held on improving the impact of HIV testing through better linkage and timely viral suppression [31]. Almost 79% of persons diagnosed with HIV are virally suppressed in King County, Washington, a number which is much higher than the national average. This is attributed, in part, to increased testing frequency, the use of sensitive tests, and high levels of treatment coverage. San Francisco General Hospital researchers described the provision of same-day, observed antiretroviral treatment to improve virologic suppression in newly diagnosed patients.

9. Special testing circumstances

During a session on special testing circumstances, Indiana State Department of Health staff described the evolution of testing strategies to improve sensitivity during an HIV and hepatitis C virus (HCV) outbreak in their state associated with injection drug use [32]. A separate presentation addressed the use of HIV-1 sequence data to infer transmission networks and inform public health action [33].

Staff from the US Military HIV Research Program presented on the impact of early treatment on subsequent disease markers. Treatment at Fiebig stage I blocked subsequent emergence of anti-HIV biomarkers commonly targeted by HIV tests while treatment at stage II delayed or decreased these serologic markers, and treatment at stages III and IV delayed or decreased seroreactivity [34]. Blood Systems Research Institute staff described the need for assays that allow for monitoring an individual’s latent HIV reservoir as we move into an era of early treatment initiation and targeted cure research [35].

A roundtable addressed the collection and use of dried blood spots (DBS), and highlighted the ease of collection and transportation of specimens, and their utility for diagnosis, monitoring and surveillance [36]. DBS can be used for HIV-1 nucleic acid testing, though the threshold for detection is lower than for plasma, in part due to lower input sample volume. DBS can also be used for drug resistance genotyping. The only U.S. diagnostic HIV

tests approved for use with DBS are an IgG-sensitive immunoassay and Western blot. A paper in this issue addresses the use of DBS: “Evaluation of dried blood spot (DBS) protocols with Bio-Rad GS HIV Combo Ag/Ab EIA and Geenius^{TM} HIV 1/2 Supplemental Assay”.

10. New tests for diagnosis, clinical staging, and surveillance

Based on the NASTAD survey, opportunities for testing for multiple pathogens are being missed: only 17% of respondents conducted HCV testing in all settings where HIV testing was provided. To test for HIV and syphilis in a hospital emergency department, separate rapid tests for each pathogen were employed at the point of care by dedicated non-emergency department staff [37]. Rapid tests are in development that detect multiple analytes. Chembio Diagnostics’ DPP HIV-Syphilis Multiplex Rapid Test detects antibodies for HIV-1/HIV-2 and *T. pallidum* [38]. BioLytical Laboratories developed a 60 s multiplex test that detects the same analytes [39]. Though the manufacturers report promising performance of these new tests, additional evaluations are needed.

A session on expanded applications of testing highlighted ongoing work to improve surveillance tools to determine rates of recent infection at the population level. CDC staff described how the switch to a BioRad Avidity assay from the BED assay and updated estimates of assay parameters were being implemented and how these changes affect population incidence estimates [40]. New assays designed to identify recent infection are in the developmental pipeline, but data are needed to determine the benefits of these new technologies [41,42]. An updated system was presented that uses routinely collected clinical data to approximate an individual’s stage of infection [43]. Finally, the Consortium for the Evaluation and Performance of HIV Incidence Assays described the potential repurposing of some assays to produce surveillance estimates for recent HIV infection [44].

11. Conclusion

The conference highlighted novel HIV testing technology, but accurate tests alone are not sufficient for improving health. Testing processes must be streamlined so that time to treatment is reduced. With respect to the recommended HIV laboratory testing algorithm, alternative tests for the second and third steps are needed that will allow laboratories to conduct all testing in the same facility. Novel technologies such as simplified nucleic acid tests can identify acute infections rapidly and may be easier to implement in a variety of settings than existing options, but hurdles exist to get tests such as these to market or to modify existing tests. Data are needed on their use in conjunction with other tests. Opportunities are expanding to synchronize testing for multiple analytes in high risk populations. Testing and linkage strategies must be examined in a variety of settings to ensure that HIV and related pathogens are identified and treated as early as possible.

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