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EXPERT REVIEWS

Insights from the 2010 HIV Diagnostics Conference

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2010 HIV Diagnostics Conference
Orlando, FL, USA, 24–26 March 2010

The 2010 HIV Diagnostics Conference brought together approximately 260 representatives from public health laboratories, test manufacturers and federal agencies for a series of test method and technology presentations, as well as policy discussions related to HIV screening in the USA. The meeting was particularly substantive in the context of moving toward a consensus laboratory testing algorithm that capitalizes on the improved sensitivities and turnaround times associated with newer technologies. This article provides a brief overview of several meeting topics, including point-of-care testing algorithms, fourth-generation immunoassays, recency testing and new technologies.

HIV testing in the USA is generally based on a combination of point-of-care (POC) rapid tests and laboratory-based *in vitro* diagnostics. A reactive initial screening test, whether a POC rapid test or laboratory-based enzyme immunoassay (EIA), requires a positive confirmatory test before an individual is considered infected. A general theme of the 2010 conference was the recognized need for updated federal guidance on HIV testing algorithms, given that the last recommendations from the US Centers for Disease Control (CDC) were released in 1989. In his opening comments, Bernard Branson (CDC) provided a timeline of testing technologies that have emerged since the 1989 recommendations. The presentation included data from Owen *et al.* at CDC, showing that essentially all approved testing technologies (including POC rapid tests) are more sensitive than western blot (WB) when evaluated in the context of test reactivity during early HIV-1 infection [1]. The cost, turnaround times and relatively poor sensitivity of the WB confirmatory test were themes in all subsequent algorithm discussions. Building on the *HIV Testing Algorithms: Status Report* released by the Association of Public Health Laboratories (APHL) and CDC in April 2009 [101], the conference was organized into sessions on POC testing, laboratory testing, recency testing and new technologies. Selected topics are briefly highlighted in the following sections.

Rapid testing algorithms at the POC

A large part of the entire first day of the conference focused on rapid testing algorithms (RTAs). A recognized problem in US screening programs is the loss of contact with individuals between an initial positive test result and the subsequent confirmatory test, particularly when confirmation is laboratory based with a turnaround time measured in days. For example, results from the State of New York showed that at least 25% of individuals with positive rapid tests failed to return for confirmatory test results. Similar statistics were reported by New Jersey, Los Angeles and San Francisco.

The focus of this compelling first conference session was the evaluation of RTAs that combine two or more rapid tests at the POC. Two specific goals of the RTAs are to more quickly establish linkage to care for infected individuals, preferably on the same day, and to alleviate issues with false positives. A general consensus among presenters was that the RTAs improved linkage to care. Counselors also indicated preference for a dual rapid test approach. Thomas Knoble from the San Francisco Department of Public Health provided specific case examples where the RTA provided client benefit. There was consensus among the presenters that the three-test RTA was not worth the added expense and quality-control overhead. A dual rapid (rapid–rapid) approach that used oral fluid–blood or blood–blood was preferred.

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In light of the slow and relatively insensitive WB-based confirmatory testing that is currently standard practice, presenters from the state and city public health laboratories made compelling arguments for the dual rapid RTAs.

There were some critiques of the dual rapid test approaches. First, orthogonality of the rapid tests was raised as a concern, since several of the approved tests in the USA may use the same antigens in their design (i.e., running a dual rapid algorithm may be repeating the same test, even if the device format is different). Furthermore, given data suggesting that some of the approved rapid tests have better sensitivity, while others have better specificity, there were questions about the sequencing of specific tests in the algorithm. Another potential complication to the dual rapid screening approach will be the availability of more sensitive fourth-generation assays, discussed in the next section.

Fourth-generation assays

From a new-technologies perspective, the session on fourth-generation assays was perhaps one of the most important of the conference. 'Fourth generation' is the term used to describe assays that combine anti-HIV antibody detection with direct detection of viral p24 antigen. The major advantage of the antigen/antibody (Ag/Ab) combination assay is that it identifies some individuals in the pre-seroconversion window phase of HIV infection. Fourth-generation assays are not new *per se*, having served as standard of care for laboratory-based HIV screening outside the USA for a number of years. However, at the time of the meeting no fourth-generation systems were currently approved for use in the USA. Although neither the manufacturers nor FDA representatives could commit to timelines, there seemed to be consensus that approval of fourth-generation systems could happen in the near future. This has been confirmed by the recent FDA approval of the ARCHITECT HIV Ag/Ab Combo assay manufactured by Abbott Laboratories [102].

Representatives from three major manufactures presented fourth-generation system descriptions and data. Kathleen Shriver from Bio-Rad described the GS HIV Combo Ag/Ab EIA and presented extensive seroconversion panel data. The lower limit of detection (LLOD) for the p24 assay was estimated at 13 pg/ml on this system using the AFSSAPS standard. Patrick Kilmartin from Ortho-Clinical Diagnostics gave a presentation on development of the VITROS® fourth-generation assay. LLOD for the p24 assay was presented at 18.4 pg/ml for the AFSSAPS standard. Barbara Kaesdorf presented the Abbott ARCHITECT® HIV-1/2 Ag/Ab Combo assay, and also reported an 18 pg/ml LLOD.

Complementing the manufacturer presentations, Mark Pandori from the San Francisco Department of Public Health Laboratory provided interesting analyses of a laboratory-based automated fourth-generation Ag/Ab system and a new Ag/Ab combination rapid test. Pandori's data were based on a panel of well-characterized recent and acute infection specimens [2]. Results were presented showing that 28 out of 35 (80%) acute infection specimens (RNA positive, negative on all antibody tests) in the collection were correctly identified with the automated fourth-generation clinical analyzer (Abbott ARCHITECT). All of these samples would be missed under current, antibody-based testing protocols. Details of this study were recently published [2].

The San Francisco group also presented an analysis of the specimen collection using a new fourth-generation rapid test. The Inverness Determine® HIV-1/2 Ag/Ab Combo is a lateral flow-based device that provides an antibody detection line analogous to other HIV-1/2 rapid tests, but also adds a separate a p24 direct antigen capture line. Pandori reported that the Determine Ag/Ab Combo appears to be at least as good, if not better, than laboratory-based third-generation EIAs for detection of HIV-1/2 antibody in seroconverted individuals. In terms of acute infection, 36 specimens in the collection were RNA positive and negative on all antibody tests. The Determine Ag/Ab Combo rapid test correctly showed 13 out of 36 as reactive (36%). While the laboratory based Ag/Ab combo assay was significantly more sensitive (29 out of 36 or 81%) than the Determine Ag/Ab combo for detecting acute infection, the fourth-generation rapid test provides a significant advantage over existing antibody-only rapids. The Inverness Determine HIV-1/2 Ag/Ab Combo test is not yet approved in the USA.

Testing for recent HIV infection

Recent HIV infection test methods were the subject of a review presentation by Michael Busch from Blood Systems Research Institute (BSRI). The window phase of HIV infection refers to the time period between initial infection and the appearance anti-HIV antibodies that can be detected by immunoassay. Detection of these recent infections is critical in blood donor settings to prevent viral transmission during transfusions and transplantation. Recency testing is also important in public health screening, as parts of the window phase are associated with very high viral loads, a period when individuals are particularly infectious. From an epidemiological perspective, characterizing HIV incidence is important for monitoring the epidemic in a population. The Busch review highlighted several approaches for recency/incidence testing, including detuned EIAs, avidity assays, antibody maturation and the BED-Capture EIA. Features of the Recent Infection Testing Algorithm (RITA) were presented. Also in this session, Kelly Curtis from the CDC presented encouraging data suggesting that anti-HIV IgG_3 may be a good biomarker for detecting recent HIV infection.

New methods & technologies

Several noteworthy presentations provided new information on test approaches. Kevin Delaney from the CDC presented a comprehensive analysis of signal/cutoff (S/CO) values for five immunoassay systems and showed that all had wide separation between true- and false-positive results. It was hypothesized that the amount of supplemental testing could be limited by incorporating analysis of S/CO data in the testing algorithm. A study evaluating EIA S/CO, presented by Rodolfo J Ochoa-Jimenez, drew similar conclusions.

Michael Busch showed that immunofluorescence assays (IFAs) dramatically reduce the number of indeterminate confirmatory results when compared with WB. The BSRI switched from WB to IFA in February 2007. Busch presented data comparing the

3 years prior to the switch to the 2 years following the switch, and showed that the IFA provided a 13-fold reduction in indeterminate rates and elimination of unreadable tests.

Robert Coombs from the University of Washington (WA, USA) provided data demonstrating that using FDA approved Bio-Rad Multi-Spot rapid test as the confirmatory to EIA allowed a 'presumptive HIV infection' result to be reported within hours of the initial reactive EIA result, reducing reporting times by a median of 2 days. Coombs also noted that the Multi-Spot identified all false-positive EIA results, and identified two out of 203 specimens as cryptic HIV-2 infection.

Several new technologies were presented. Timothy Granade from the CDC provided results for p24 antigen and HIV-1 and -2 antibody detection using a novel, POC magnetic immunochromatography system. The p24 assay was particularly encouraging, with LLOD near 30 pg/ml, making it competitive with laboratory-based fourth-generation assays. Very high-sensitivity detection of p24 antigen using europium nanoparticles was also presented by Shixing Tang from the US FDA. Michael Lochhead (mBio Diagnostics, Inc.) presented data for a combined HIV-1/syphilis assay using the POC SnapEsi™ system, which combines a disposable cartridge with a simple fluorescence reader and provides a multiplexed panel of results for a single POC sample. John Kim from the Public Health Agency of Canada presented a novel method for creating molecular controls for viral load assays, a particularly acute need in the context of HIV-2 detection. Marco Schito from the National Institute of Allergy and Infectious Diseases at the NIH provided an overview of several technologies focused on POC viral load assays. These included technologies under development at Wave80 Biosciences, Diagnostics for the Real World and Advanced Liquid Logic.

Moving toward a unified laboratory algorithm

The conclusion of the meeting focused on a discussion of a revised testing algorithm recommendation. In a preliminary proposal widely applauded by attendees, Bernard Branson provided a preliminary unified laboratory algorithm that would recommend use of the 'most sensitive' available assay for the primary screen. This initial screen will likely be a fourth-generation EIA, once tests are approved by the FDA. A reactive screening result will then be reflexed to a confirmatory test that preferably discriminates HIV-1 versus -2. The use of rapid tests for confirmation was part of the discussion. Finally, a negative confirmatory test (i.e., discordant (+) screen/(-) confirmatory) would be reflexed to nucleic acid amplification testing. A positive nucleic acid amplification testing result would then be indicative of infection.

The consensus around moving away from WB confirmatory testing was a major feature of the conference close. It was noted that WB still provides valuable information and will be an important tool for clinicians and laboratorians, but that alternative confirmatory tests make good public health sense from nearly all perspectives, including test quality, turnaround time and cost. Finally, new technologies appear to be on the horizon that provide the antigen-specific information of WB, but in a more quantitative, lower cost package. A multi-line lateral flow device currently available as a confirmatory test in Brazil was highlighted as an example.

Conclusions

The 2010 HIV Diagnostics Conference provided a vigorous exchange of public health data, new technologies and policy concepts. The CDC/APHL organizing committee should be congratulated for presenting a excellent mix of topics. Practical movement toward new federal recommendations for HIV testing in the USA appears to be a major outcome of the conference.

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