Algorithm for HIV testing detects more cases, more quickly

William Check, PhD

December 2013—Screening to detect HIV infection is poised to make a leap into the 21st century. In his presentations on the proposed new screening algorithm, Bernard M. Branson, MD, points out that in 1989, when the now outmoded algorithm was recommended, the telephone booth was a common sight and the "portable" computer was the size of a small suitcase. Dr. Branson, associate director for laboratory diagnostics in the Division of HIV/AIDS Prevention at the Centers for Disease Control and Prevention, also points out that 1989 was the year of the dismantling of the Berlin Wall and the Tiananmen Square massacre.

"It is clear that we need an updated algorithm," Dr. Branson told CAP TODAY. One major problem with the old algorithm is that the sensitivity of the third- and fourth-generation enzyme immunoassays for HIV that are now available surpasses the performance of the confirmatory Western blot. Some contemporary EIAs turn positive as many as 25 days before the Western blot, so the latter may fail to confirm specimens with true infection.

Dr. Branson

"There has been increasing recognition that EIAs currently in use by laboratories all detect HIV infection earlier than the Western blot is able to confirm," Dr. Branson says. "And there is preliminary evidence that some people repeatedly reactive on these newer assays have negative and indeterminate Western blots. As a result, laboratories may interpret specimens as negative, even though those people have viral RNA that can be detected on molecular assays."

Another important reason to alter the screening algorithm is to be able to detect HIV infection in the acute stage, the first three months, when the patient has high levels of circulating virus and is highly infectious, yet has no circulating antibody and no specific symptoms. Current treatment guidelines recommend starting therapy as early as possible after infection, and starting in the acute stage would be optimal.

Nathan A. Ledeboer, PhD, D(AB-MM), agrees that "The [proposed] new algorithm recognizes the development of improved immunoassay technology and the importance of discriminating between HIV-1 and HIV-2, as well as the early diagnosis that nucleic acid tests can provide." Differentiating HIV-1 from HIV-2 is important because drugs used to treat HIV-1 are not effective against HIV-2. Earlier diagnosis means earlier treatment.

Dr. Ledeboer

“The most recent data coming out of management of HIV patients suggests that getting them on highly active antiretroviral therapy as early as possible in the course of their disease will significantly reduce their chances of developing a later AIDS-associated or AIDS-defining illness,” says Dr. Ledeboer, associate professor of pathology at the Medical College of Wisconsin and medical director of clinical microbiology and molecular diagnostics in the Dynacare Laboratories and Froedtert Hospital. He and colleagues are converting now from the 1989 algorithm to the new proposed algorithm. “We want to change to a fourth-generation EIA. The holdup is that only two vendors have FDA clearance and we need to get a new instrument.”

In addition to adopting the new algorithm, Froedtert Hospital exemplifies another important trend: doing HIV screening in places other than publicly funded sites, consistent with the CDC’s 2006 recommendation calling for HIV screening in health care settings generally (Branson BM, et al. MMWR. 2006;55[RR14]:1–17). “Where we encounter HIV patients has changed,” Dr. Ledeboer says. “Many present about once a year and don’t get care in traditional settings, such as a physician’s office. Instead they go to the emergency department or to walk-in or urgent care clinics. If we don’t offer testing where we encounter patients, we will be ineffective in detecting these infections.”

According to Dr. Branson, reimbursement should not be an issue. “Things are changing with the Affordable Care Act,” he says. And this past summer the U.S. Preventive Services Task Force gave HIV screening a grade A recommendation, making screening for 13- to 65-years-olds reimbursable by insurers with no copay.

A study done by the New York City Health and Hospitals Corp. and reported in early November demonstrates the impact of screening programs in such settings. In 2005 the NYC HHC began offering routine HIV testing throughout the care sites of its 11 acute-care hospitals and six large-scale community clinics. From 2005 to 2012, the proportion of age-eligible patients screened doubled, from 9.4 percent to 18 percent, and the rate of concurrent HIV/AIDS diagnosis for newly diagnosed patients dropped from 32.3 percent to 25.3 percent. Data from these sites showed that when more than 20 percent of patients are screened, the yield of new HIV diagnoses levels off at about 0.3 percent. Moreover, trend analysis suggests that concurrent HIV/AIDS diagnosis can be avoided when 40 percent of patients are screened annually, says Eunice Casey, assistant director of HIV services at the NYC HHC.

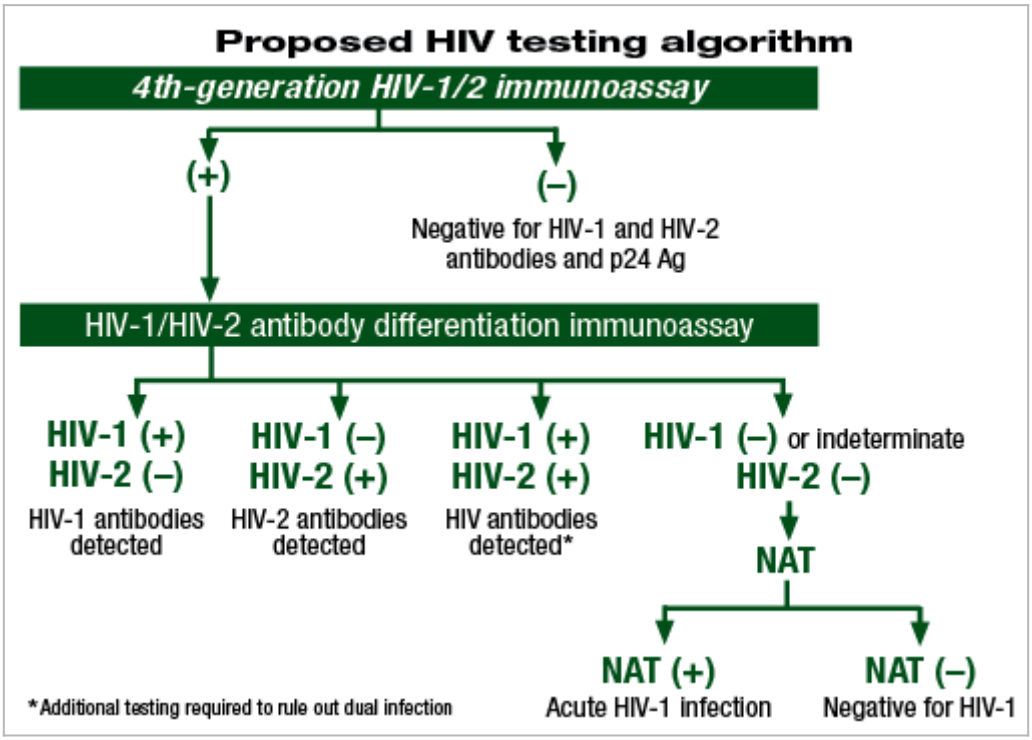
The CDC and Association of Public Health Laboratories proposed a new algorithm in 2010 “based on theoretical considerations,” Dr. Branson says (Branson BM. J Acquir Immune Defic Syndr. 2010;55 Suppl 2:S102–105). Initial screening is performed with a fourth-generation HIV-1/2 EIA. Positive samples go to an HIV-1/HIV-2 antibody differentiation assay. Detection of antibody to either strain leads to a positive diagnosis. Samples that are HIV-1 negative or indeterminate and HIV-2 negative on the differentiation assay are tested with a nucleic acid test. Positive samples are diagnosed as acute HIV-1 infection; negative samples are declared HIV-1 negative. (See page 42.)

The algorithm was initially evaluated clinically with third-generation assays, since the first fourth-generation assay was not approved until June 2010. Third-generation EIAs detect both IgG and IgM antibody; fourth-generation assays detect p24 antigen as well. Third-generation assays turn positive about 22 days after infection, fourth-generation assays at around 17 days; this represents 15 and 20 days before Western blot, respectively (Masciotra S, et al. J Clin Virol. 2011;52 Suppl 1:S17–22). RNA assays turn positive at about 10 days after infection, 27 days before Western blot.

Casey

Approval was also needed to use the differentiation assay, the MultiSpot HIV-1/HIV-2 rapid test, in the diagnostic algorithm. Specifically, approval was needed for an indeterminate category for the differentiation assay, which is different from when it is used as a rapid test. Approval for this category came in March. “So we needed evidence and appropriate FDA indications to allow labs to use these tests in the algorithm,” Dr. Branson says.

“Several evaluations showed that the performance of the proposed algorithm with third-generation assays was better than the old algorithm,” Dr. Branson says. For example, investigators in the Masciotra study found that, among seroconverters, the proposed new algorithm “detected significantly more infections than the current algorithm (103–134 versus 56).” In this study, screening with a fourth-generation assay was superior to the third-generation assays tested, particularly for detecting acute infections.



In a retrospective validation study conducted in the New York State Department of Health, the new algorithm identified 32 more people who were HIV positive (out of 1,578) than the current algorithm. It also produced fewer inconclusive results (nine versus 48), while requiring 112 fewer tests (Styer LM, et al. J Clin Virol. 2011;52:S35–S40). Thus, the new algorithm was more effective and more efficient.

“It is now necessary to validate the proposed algorithm with fourth-generation assays,” Dr. Branson says. “We are still accumulating prospective data.” During a 12-month implementation period in Massachusetts, the new algorithm incorporating a fourth-generation EIA detected eight acute infections, six of which were not detected by a third-generation EIA. This result is in line with validation studies of the two fourth-generation EIAs showing that they detect 83 percent to 89 percent of acute infections.

Detecting HIV infection during the acute stage is a major advantage of the more sensitive assays in the new algorithm. Among men who have sex with men tested at public health sites in Seattle, a first- or second-generation EIA detected 169 infections. (A rapid test detected 153 of these.) An additional 23 positive samples—12 percent of the total 192 positives—were detected only by RNA testing (Stekler JD, et al. Clin Infect Dis. 2009;49:444–453). When 16 of these 23 samples were tested with a fourth-generation EIA, 15 were positive.

“While the prevalence of acute infection overall is relatively low,” Dr. Branson says, “acute infection represents a substantial proportion of the people who are infected at the time tested. These people would receive a negative test result by the current algorithm.” Detecting acute infection is important because patients are much more infectious at this time. During the three-month acute stage of infection, the transmission rate is 2.8, compared to 0.1 during the subsequent long, asymptomatic phase (Hollings-worth TD, et al. *J Infect Dis*. 2008; 198:687–693).

Beginning treatment as early as possible in the course of the infection produces the best outcomes (Cohen MS, et al. AIDS. 2012;26: 1585-1598).

“The new algorithm needs to be vetted for acceptability and applicability with various stakeholders, including CAP. We at CDC are moving the recommendation but waiting for peer review.” He says the CDC will continue to accumulate validation data as the algorithm is being adopted and continue to evaluate other tests for inclusion in the algorithm as they receive FDA approval.

During a CAP ’13 presentation, Dr. Branson asked those in the audience what methods their laboratories were using. “I was surprised to see that a good percentage had already begun moving in this direction,” he says. FDA approval of the MultiSpot differentiation assay in March enabled labs to adopt the whole algorithm, he says. “Because this test is of moderate complexity, it can be done in a much broader range of labs and with a faster turnaround time than Western blot, which for many labs was a sendout.” One worry for Dr. Branson: “Some labs were still reporting negative or indeterminate results based on Western blot in samples that were repeatedly reactive with an initial more sensitive immunoassay.”

Dr. Ledeboer endorses the recommendation to test more broadly in health care settings. Seventy-five percent of those who are HIV-infected have received a diagnosis, and the challenge is to identify the remaining 25 percent, he says, adding, “We need to test where the patients are.” He cites an analysis of U.S.-based emergency department HIV testing conducted from 1993 to 2005. An average of 3.2 tests per thousand visits was performed. “The rather interesting result from this,” Dr. Ledeboer says, “was that six percent of the tests were positive. If we compare this to testing in a traditional physician office, we have a less than one percent positivity rate.”

More people will be tested if screening is made opt-out rather than opt-in. In the past few years, Dr. Ledeboer says, Wisconsin has removed the requirement that a separate written consent is needed to test for HIV, eliminating one barrier to wider screening.

Getting the result to the patient is as important as testing itself. Dr. Ledeboer cites a 1999 figure that 25 percent of those who tested positive at publicly funded clinics did not return for test results. “If a person is at risk of not following up, maybe you can screen with a rapid test,” he says.

Point-of-care HIV testing is becoming more prevalent, and many rapid tests with excellent sensitivity and specificity are available. “Papers evaluating the performance of the new algorithm using rapid tests show excellent performance,” Dr. Ledeboer says.

One of the most common questions he has been asked is what to do when a person is positive on a rapid test. The proposed new guidance recommends using the proposed algorithm, starting with a fourth-generation assay, after a reactive rapid test. Next in the new algorithm is an HIV-1/2 differentiation assay and an HIV-1 RNA test for confirmation.

A laboratory, too, might use a rapid test. “Choice of a screening test will vary based on volume and the turnaround time needed,” Dr. Ledeboer says. The laboratory he directs at Froedtert Hospital has enough volume to set up a fourth-generation EIA. Childrens Hospital next door, which does a lower volume of testing, uses only rapid tests. “They test mainly two groups of people: employee exposures and pregnant women with no prenatal care.” A rapid test costs $15 to $17, whereas highly automated third- and fourth-generation EIAs cost a few cents to $3 to $4.

Hamilton

In the New York City Health and Hospitals Corp. program, the goal is to continue to increase the proportion of persons screened. Today, eight of the 17 facilities screen 20 percent or more of patients ages 13 and over, and some have screening rates in the high 30 percent range. “We have a baseline annual target of 20 percent of age-eligible persons screened at all facilities,” says director of HIV services Terry Hamilton. “Each year one or two more exceed that target.”

To increase screening rates further, Hamilton says, “I believe very strongly in our effort to create a system of routine testing that does not depend on any single individual. We want to get away from depending on individual goodwill in a sense to a reality that this is an ordinary part of the medical visit.”

New York state mandates the offer of HIV testing through an informed consent process. “We have been able to manage [informed consent] expeditiously,” Hamilton says, “by using information technology to make it easier for providers to offer and perform HIV screening.”

To get away from reliance on individuals, the individual aspects of the HIV screening process can be divided among care-team members, assistant director Eunice Casey says. “So a single provider is not responsible for doing informed consent, acquiring a sample, and the other tasks in this process. We want to integrate HIV screening fully into wherever we are working, whether it is in the ED, inpatient, or ambulatory care. We want to make it as streamlined as possible.”

Additional tests that are approved or under evaluation will provide more options for the screening algorithm. One rapid test Dr. Branson mentions is the Alere Determine HIV-1/2 Ag/Ab Combo, which was approved in August. “So far we don’t have much U.S. data on its performance,” he says. Still in clinical trials is the Bio-Rad Geenius HIV-1/2 rapid test.

“The new algorithm recommends classes of tests. So it recommends a fourth-generation EIA, not the Abbott Architect,” Dr. Branson emphasizes. For now, the only differentiation assay is the MultiSpot. If approved, the Geenius will offer laboratories an alternative for this function.
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