

MINIREVIEW

Home Testing To Detect Human Immunodeficiency Virus: Boon or Bane?

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With the waiver of the Orasure Oraquick rapid human immunodeficiency virus (HIV) test in January 2003, testing for HIV infection in the United States moved from the laboratory to the clinic, the emergency room, and other outpatient settings. By now, millions of rapid HIV tests have been performed, largely by nonlaboratorians and largely outside of dedicated laboratory space. This experience has significantly transformed HIV testing nationally. The next logical step in broadening the settings in which HIV testing can be performed, approval of an HIV test for sale “over the counter” (OTC), involves clinical, technical, psychological, and public health issues along with a fair sprinkling of politics.

Much of the rationale for both rapid, “waived” and home-use HIV testing can be summarized by two simple statistics: (i) approximately 30% of HIV-infected persons in the United States are unaware of their serostatus, and (ii) in 2004, 39% of persons with AIDS (e.g., opportunistic infection or CD4⁺-T-cell count of <200) first tested positive for HIV within 1 year of their AIDS diagnosis (7).

Current evaluative approaches are missing substantial numbers of infected persons and detect HIV infection at a later stage than is optimal. Expanding access to HIV testing is a logical approach to addressing these inadequacies. Newly proposed methods for HIV testing must be compared not with an ideal system but with the current state of HIV surveillance and testing.

In the United States, kits for home diagnostic testing are available for a limited set of analytes (9). There are currently no OTC tests for infectious diseases; tests for group A streptococcal pharyngitis and for influenza were rejected for home use due to insufficient sensitivity. There are, however, home *collection* kits for hepatitis C virus and HIV infection that allow consumers to collect specimens and send them to laboratories for testing and direct reporting.

The scientific literature on home testing has recently been reviewed and can best be described as “sparse” (12). There have been few studies of the accuracy of home testing methods beyond those performed for Food and Drug Administration (FDA) approval. Even for well-established practices such as home glucose monitoring, there are limited data with respect to outcomes: the recommendations of the American Diabetes

Association and the World Health Organization are based primarily on cohort studies and expert opinion and not on controlled studies showing a clinically significant impact on outcomes. The randomized clinical trials that have been performed demonstrated mixed results; a few showed improvement in outcome measures such as hemoglobin A1c levels, but more trials showed no significant effects. Although tests are widely available, an estimation of the clinical or public health impact of *any* home testing method is nearly pure guesswork at this time.

RAPID, WAIVED HIV TESTING

Clinical Laboratory Improvement Amendments-waived tests are considered by the FDA and Centers for Medicare and Medicaid Services to be so simple to perform that their use carries little risk of erroneous results. All home-use tests are waived, although not all waived tests are approved for home use (2). The two waived HIV tests, the Oraquick HIV 1/2 and the Trinity Unigold tests, are both lateral-flow immunochromatographic methods. The Oraquick test is approved for whole blood, serum, plasma, and oral fluid; the Unigold test is approved for whole blood, serum, and plasma. For the Oraquick test, the waived status applies only to oral fluid and whole-blood specimens; for the Unigold test it applies only to whole blood. The following descriptions, condensed from the package inserts of the two kits, demonstrate the complexity (or simplicity, if you prefer) of the methods in their current forms.

Procedure for the Orasure Oraquick Advance HIV 1/2 test. To perform an Oraquick test, the test subject collects blood from a finger stick site with a collection loop and transfers it into a developer solution vial. Alternatively, for oral fluid specimens, the subject swabs the outer gums, both upper and lower, using a flat pad on the test device. The test device is then placed into a developer solution vial. Test results are interpreted between 20 and 40 min after placing the test device into the developer solution vial. A reactive test will display a red-purple test line in the presence of a positive control line, and a negative test will show only the control line (Oraquick Advance Rapid HIV 1/2 Antibody Test package insert; Orasure Technologies, Inc.).

Procedure for the Trinity Unigold Recombigen HIV test. For the Trinity Unigold Recombigen HIV test, a blood sample is collected using a disposable transfer pipette. The pipette tip is applied horizontally to a finger stick site, and blood automatically flows into the pipette. Samples that fail to reach the

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volume indicated by a gradation mark on the pipette must be discarded. After the specimen has been collected, it is discharged into the device's sample port, followed by the application of 4 drops of wash solution. Test results must be read at an incubation time of between 10 and 12 min. A red color in the sample port verifies proper device loading, a control line verifies proper device operation, and the presence or absence of a test line provides a positive or negative result (Unigold Recombigen HIV package insert; Trinity).

Performance of current rapid HIV tests. Data presented to the FDA in support of approval indicate that when performed by trained personnel, rapid HIV tests have sensitivities and specificities comparable to those of conventional enzyme immunoassay (EIA) methods for seroconversion panels, low-titer panels, high- and low-risk unknown panels, and known positive and negative specimens (3, 4). Other previously published studies have demonstrated that rapid HIV tests perform similarly to laboratory-based EIA methods (1, 11).

In the largest of such studies, the Mother-Infant Rapid Intervention At Delivery trial, HIV testing with Oraquick in labor-and-delivery units had a sensitivity equal to that of laboratory-based EIAs, with fewer false-positive results (1). Another study that assessed the rate of performance-related errors in the use of two rapid HIV tests by nonlaboratorians found a significant number of errors related to sample handling, inoculation, and also record keeping. These former errors are relevant to the actual performance of a home-use test, while the latter are probably not. Error rates declined when study participants were given a test demonstration, leading those authors to emphasize the need for effective training in the basic operation and interpretation of rapid HIV tests (11).

In conjunction with the waiver of rapid HIV tests, the CDC issued performance and quality assurance guidelines. These guidelines were recommended for all health care organizations that perform rapid HIV testing (5). It should be mentioned that some testing sites have seen clinically significant (and occasionally well-publicized) false-positive results with rapid HIV tests, most notably when testing fluids using the Oraquick method (10). This has led a few sites to discontinue rapid HIV testing. Nevertheless, the overall performance of rapid HIV tests has been consistent with stated specificities well above 99%. These tests have been widely deployed; the CDC alone distributed 790,310 rapid test kits between September 2003 and December 2005 (6).

REGULATORY HISTORY AND PROSPECTS FOR HOME HIV TESTING

HIV testing products in the United States are evaluated for approval by the FDA's Center for Biologic Evaluation and Research (CBER). The CBER is advised on matters relating to HIV testing by the Blood Products Advisory Committee. The FDA has considered approval of home HIV testing, including both collection kits and test kits, during the past two decades (9). Discussions have reflected changes in HIV testing technology, treatments, and social attitudes toward HIV as well as concerns about the accessibility of some testing for at-risk groups, the provision of adequate counseling, the maintenance of confidentiality, and the effectiveness of education and follow-up. After considerable debate, in 1995, the FDA

expressed a willingness to approve home specimen collection kit systems (8).

Subsequently, point-of-care HIV test kits that have a very low risk of giving incorrect results, are simple to use, do not require special storage conditions, provide results within 20 min, and, in one case, use oral fluid as a specimen have been developed, limiting concerns about biohazardous conditions. There is now substantial experience with these tests in nontraditional settings. The state of the art in HIV therapeutics supports the hypothesis that early detection leads to better clinical outcomes. It has been argued that these factors, in addition to changes in social awareness of HIV infection, favor the approval of a home test. The FDA held public hearings on home-use HIV tests on 3 November 2005 and on 10 March 2006. Extensive documentation of both hearings is available online at the FDA web site (<http://www.fda.gov/ohrms/dockets/ac/cber05.html#BloodProducts> and <http://www.fda.gov/ohrms/dockets/ac/cber06.html#BloodProducts>, respectively).

November 2005 hearings. In the November 2005 hearings, major arguments presented in favor of the approval of home-use HIV tests included anonymous testing, which will likely increase awareness of HIV status; earlier diagnosis and treatment; consumer empowerment in health care decisions; the potential to positively impact high-risk behavior and public health; the possibility that home-use HIV test kits would destigmatize and routinize testing; and their particular suitability for young people, who often prefer to avoid formal test settings.

Concerns put forth that weigh against approval include possible inappropriate test use, e.g., after very recent exposure; improper performance or interpretation of the test by untrained persons; adverse psychological outcomes from testing without counseling; testing without reporting of results to public health authorities; testing without follow-up and partner notification; coercive testing; testing by minors without adult involvement; acceptance of positive results without confirmation, particularly in low-risk populations in which false-positive rates could be high; and limited test availability for high-risk populations and possible negative impact on other screening programs.

Other objections to approval were the potential impropriety of having untrained individuals performing tests for an infectious agent that has significant individual and public health implications, testing outside of a "quality system" structure, and the tendency of adolescents to seek testing during the "window period" after high-risk encounters, when false-negative tests can occur.

It is noteworthy that no significant increase in suicide risk has been observed in association with the transmitting of positive HIV test results to patients. Moreover, the reporting of negative HIV test results has been associated with relief of stress. Conversely, adverse psychological reactions to positive test results are associated with fear and lack of knowledge. Arguably, patient knowledge is likely to be greater when testing is performed in a health care setting, as opposed to the home.

Other questions raised in relation to the approval of home-use HIV test kits were as follows: Who will most likely use such a test? How will sales of a home-use HIV test kit to inappropriate entities be prevented? What will the impact of such a

test be on public health testing and reporting? How will the possible diagnosis of new HIV infections impact overloaded treatment programs? Who will perform the postmarketing studies needed to assess safety, posttest behavior, effectiveness of written materials, and frequency of appropriate medical follow-up?

At the hearing, Orasure Technologies, Inc., proposed offering a home-use test kit based upon its Oraquick test. In addition, the manufacturer also suggested performing studies to prove the ease of use and accuracy of a home-use HIV test. Representatives of the CDC described that agency's positive field experience with the Oraquick test, described quality systems for home-use diagnostic tests, and presented information on significant quality problems in waived testing derived from surveys of Clinical Laboratory Improvement Amendments-waived laboratories.

According to the FDA, a home-use HIV test is expected to be "at least as accurate as a comparable waived product." Analytical sensitivity and specificity, using the true infectious state as the "gold standard," must be high. However, the FDA can be flexible on performance levels in the intended-use population. As stated by the FDA, "if requirements for performance are unattainable, then the availability of a home-use test kit would be jeopardized." It is unclear how these statements are to be reconciled.

Finally, package inserts should clearly discuss test performance, including sensitivity, specificity, positive predictive values for key populations, and reasons for false-positive and false-negative test results. Literacy studies should be performed, and pictorial package inserts should be considered. Validation of informational materials could be similar to that for blood donor questionnaires.

In conclusion, in order to obtain approval from the FDA for OTC sale of a test kit, a manufacturer must demonstrate that the device is accurate and reliable in the hands of lay users, that the device is adequately labeled to convey all information necessary to use the device safely and effectively, and that the benefits of approving the device outweigh the risks.

March 2006 hearings. The March 2006 hearings focused on the field performance of current rapid HIV tests and the studies that should be required for approval of an OTC HIV test. Several speakers urged that any performance targets for a home-based test should take into account the likely public health impact of increased access. In contrast, the American Society for Microbiology representative expressed concerns about the quality of unsupervised testing and asked that the potential harm of both false-positive and false-negative test results be assessed in the absence of pre- and posttest counseling.

Some phase I study data dealing with the performance of the proposed tests in skilled hands are already available in approval and waiver applications. Additional phase I data recommended by the FDA include operational stress ("flex") studies that assess the ability of tests to withstand errors and mishandling without giving erroneous results. Phase II studies are expected to involve subjects from groups likely to use the products. These studies would involve self-testing as well as the evaluation of positive, negative, and weakly positive known specimens. The FDA recommended at least three geographically diverse clinical trial sites with high HIV prevalence.

The FDA is considering ways to address the issue of phase III trials. Option 1 resembles the phase II studies. In this case, a comprehensive evaluation of both self-testing and testing of known specimens as well as the evaluation of instructional materials and the counseling and referral system would be performed. Option 2 is limited to the evaluation of the instructional materials and counseling system without actual testing, based on the assumption that phase II test performance is sufficient for validation. Option 3 is that no additional requirements would be imposed upon manufacturers beyond the phase II studies.

Extrapolating from past experience and the discussions at the March and November meetings, it seems likely that in the near future, the FDA will offer issue-specific guidance to the industry on the requirements for validation of a home-use HIV test. This will represent a "road map" to approval of a home-use test. Manufacturers will need to perform required studies and present the data to the FDA for analysis and decision, but approval of a home-use HIV test within the next few years appears to be a distinct possibility.

HOME-USE HIV TESTS: POTENTIAL IMPACT

Home-use testing can potentially improve *access* to testing services for at-risk individuals. This in turn is expected to result in the earlier diagnosis and treatment of HIV infection, positively influence risk behaviors, and empower consumers to control their own health care. Conversely, the major concerns regarding home-use testing are test accuracy, error, and misuse.

It is certain that a home-use test will allow persons who otherwise go untested to self-test both for early detection and to modify their risk of acquiring HIV. It is equally certain that self-testing will be less accurate and more prone to misinterpretation than testing that is performed by a health care professional who also conveys the results and counsels the patient about their significance. Balancing the benefit of access against the risk of error is a complex, subjective calculation for which there are little available data. To clarify the issues, it is instructive to imagine "best-case" and "worst-case" scenarios for approval of a home-use test.

In the worst case, a rapid HIV test would be approved, but the real-world accuracy in the hands of intended users would be less than intended. The test would be expensive and heavily and widely marketed beyond high-risk groups. False-positive tests would be frequent in low-risk populations where inappropriate self-testing would become common. In high-risk populations, the test would instill a false sense of security, exacerbated by false-negative results and a poor understanding of the limitations of the test. Transmission would increase in some groups, especially young people during the highly infectious window period. Positive and negative tests could be misinterpreted, and persons needing care may lack the resources to find it. Other testing resources and programs might be harmed by competition with the OTC test, and access for underserved populations overall may be harmed and not improved.

In the *best* case, a rapid HIV test that is economical, selectively marketed to at-risk persons, and accurate in untrained hands would be approved. Persons who would otherwise go untested would self-test, and most who are infected would be

directed to early care and prevention resources. Persons engaged in risky behavior would utilize self-testing to reduce their risk of acquiring HIV. Overall, there might be a reduction in HIV transmission and an increase in the early diagnosis and treatment of HIV disease.

Whether or not one favors FDA approval of home HIV tests is largely dependent on one's estimates of the likelihood that either of these scenarios will occur or where on the continuum between them the reality will lie. Given the lack of published data on the impact of other home tests, one concern is whether outcomes can be accurately assessed. Innovative approaches to measuring the impact of a home HIV test, if approved, are urgently needed.

The clinical laboratory community can contribute to the debate on home HIV testing in several ways. As experts on quality diagnostic testing, we can remain engaged through our professional organizations not only in the controversy over approval or nonapproval of a home test but also in the details of what should be required for a test to be approvable and how to validate a candidate system. Given both the state of the current process and the availability of other high-impact analytes in a home format, simply stating that laboratory testing should be performed only by laboratory professionals seems inadequate and self-defeating. Clinical laboratory professionals need to be engaged in educating the public on the realities of diagnostic testing; advocating for careful, realistic assessment of potential tests; comprehensively evaluating the potential impact of home tests; and advocating research on the

overall health impact of home HIV tests if approved as well as of other home testing methodologies.

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