Rapid HIV Tests: Federal Regulatory Action Changes HIV Testing Landscape

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A recent flurry of federal regulatory action on rapid HIV tests has transformed the landscape of HIV-antibody detection in the United States. The first rapid test in the United States received Food and Drug Administration (FDA) approval in late 2002. By the beginning of this year, a total of 4 rapid tests were approved for sale in the United States; of these, 2 were cleared for use outside traditional laboratory settings (**Table 1**). The 4 rapid HIV tests with FDA approval are:

- OraQuick Advance Rapid HIV-1/2 Antibody Test, manufactured by Orasure Technologies and distributed by Abbott Laboratories;
- Uni-Gold Recombigen HIV Test, manufactured by Trinity Biotech plc and distributed by Fisher Scientific;
- Reveal G2 Rapid HIV-1 Antibody Test by MedMira, distributed by Cardinal Health; and
- Multispot HIV-1/HIV-2 Rapid Test, made and distributed by Bio-Rad Laboratories.

Of the 4 rapid tests with FDA approval, 2 are waived from certain requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (**Table 2**). These are:

- OraQuick for whole blood and oral fluid specimens; and
- Uni-Gold for whole blood specimens.

CLIA waivers are issued for tests that are simple and accurate enough that there is little risk of receiving an incorrect result, so the tests need not be performed in laboratories certified for moderately complex testing. Laboratories performing CLIA-waived tests must enroll in the CLIA program, pay a biennial fee to obtain a Certificate of Waiver; and follow manufacturers' test instructions. In the case of rapid HIV tests, CLIA waivers enable rapid testing to be performed in 5 times as many facilities, including physicians' offices and outreach clinics that more readily reach high-risk populations.

Beginning in the mid-1980s, HIV antibody was detected using enzyme immunoassay (EIA), primarily to screen donated blood to protect the blood supply. Voluntary counseling and testing services then began using the EIA to determine the status of high-risk individuals. Positive results were then confirmed using Western blot. The EIA-Western blot series was long considered the gold standard for HIV antibody detection, but eventually the need for same-day results became paramount, especially in developing countries and public health settings in the United States. Results from sensitive EIAs may take 3-4 days, whereas results from rapid tests may be available in 10-20 minutes.

According to the Centers for Disease Control and Prevention, an estimated 850,000 to 950,000 people are infected with HIV in the United States, and 180,000 to 280,000 are unaware they are infected. About 40,000 people a year become infected with HIV in the United States. In public health settings offering traditional HIV testing, 30% to 40% of patients do not return for their test results. Of about 2 million publicly funded HIV tests conducted each year, 6,000 to 8,000 patients never find out they are infected.

"Rapid HIV testing greatly improves the percentage of patients who learn their test results," wrote authors Drs. Patrick Keenan and Joseph Keenan of the University of Minnesota Medical School and Dr. Bernard Branson, associate director of laboratory diagnostics in CDC's National Center for HIV, STD, and TB Prevention, in "Rapid HIV Testing: Wait time reduced from days to minutes," in the March 2005 issue of *Postgraduate Medicine*. Furthermore, "the result (from rapid tests) is comparable in clinical significance to a sensitive EIA (enzyme immunoassay) result."

Table 1_Recent Regulatory Action on Rapid HIV Tests

Date	Action	Test	Sample Type
November 2002	FDA approval	OraQuick Rapid HIV-1 Antibody	Whole blood
December 2003	FDA approval	Uni-Gold Recombigen HIV	Serum, plasma, whole blood
March 2004	FDA approval	OraQuick Rapid HIV-1 Antibody	Oral fluid
	FDA approval	OraQuick Rapid HIV-2* Antibody	Whole blood
June 2004	CLIA waiver	OraQuick Rapid HIV-1/2* Antibody	Whole blood
(finger stick & venous), oral fluid	FDA approval	Reveal G-2 Rapid HIV-1 Antibody	Serum, plasma
September 2004	FDA approval	Uni-Gold Recombigen HIV	Whole blood
(finger stick)			
November 2004	CLIA waiver	Uni-Gold Recombigen HIV	Whole blood
(finger stick & venous)	FDA approval	Multispot HIV-1/HIV-2* Rapid	Serum, plasma

**HIV-2 is most prevalent in Africa, particularly West African nations. Because few cases of HIV-2 infection in the United States have been documented, testing in the United States tends to focus on HIV-1.*

Table 2_FDA-Approved, CLIA-Waived Rapid HIV Tests

Test/Specimen	Sensitivity	Specificity	Time to Result	Screens for
OraQuick Advance/				
Whole blood	99.6	100	20 min	HIV-1 and 2
Oral fluid	99.3	99.8	20 min	HIV-1 and 2
Uni-Gold Recombigen/				
Whole blood	100	99.7	10 min	HIV-1

Source: "Rapid HIV Testing: 2005 Update," a presentation by Bernard M. Branson, MD, associate director for laboratory diagnostics, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Department of Health and Human Services

Testing and Social Stigma

The importance of counseling people before and after HIV testing may play a deciding factor in whether rapid HIV tests comparable to over-the-counter (OTC), at-home pregnancy tests are ever submitted to and approved by the FDA for sale in the United States. The agency's review and approval process for such an application would consider whether the user would get acceptable results from the test compared to those obtained when a professional performs the test, whether the user would be able to interpret test results correctly, and whether the benefits of the test outweigh its risks.

Dana E. Thomas, director of marketing for Trinity Biotech, said the evolution of rapid tests for HIV is similar to that of OTC pregnancy testing. "The reason it took so long (for pregnancy tests) to get into the OTC market were exactly the same that are facing HIV right now," he said. "It was the social dilemma of what a woman would do with a positive pregnancy test at home. It's exactly the same here: What would a person do with a positive HIV test at home without proper counseling and direction?"

To date, the FDA has approved 1 at-home collection kit, Home Access HIV-1 Test System, manufactured by Home Access Health Corp. The Home Access test system is sold directly to consumers, but it is not a rapid test. Approved in 1996, the kit contains materials needed to collect a blood specimen and to it to a laboratory qualified to perform an EIA test. Clients receive a booklet instructing them to call a toll-free number to register the code number provided in their kit. During the call, the clients are asked to provide basic demographic data and to listen to a 5-minute recording about the test, HIV prevention, risk reduction, and AIDS. Counselors are available to clients by phone at all times before and after sample collection any day of the year except holidays. Test results are available to the client within 3 days with the "express" kit and 7 days with the standard kit. Since 1997, the FDA has issued at least 15 warning letters to other companies selling unapproved home HIV test kits.

Thomas believes that in the future EIA will be the staple for screening the blood supply, which was its original purpose. "Virtually everywhere else, rapid tests will be the standard norm for testing for HIV, and it makes perfectly good sense," he said. "Outside of the blood bank environment, everywhere else you'd want to know that result as quickly as possible. You want it with a test that's simple, easy, and extremely accurate."

How They Work

Among the CLIA-waived rapid tests, OraQuick involves obtaining a drop of blood through finger stick or venipuncture, inserting and stirring the specimen in a vial of solution, inserting the test device into the solution, and reading the results in 20 minutes. With Oraquick's oral fluid specimen test, the gums are swabbed with the test device, which is then inserted into the solution; test results are available in 20 minutes.

According to Orasure's device description submitted to the FDA, OraQuick uses a proprietary lateral flow immunoassay procedure. The device holds an assay test strip comprised of several materials providing the matrix for the immunochromatography of the specimen. The strip contains synthetic peptides representing the HIV envelope region. As the diluted specimen flows through the device, it rehydrates the protein-A gold colorimetric reagent. If the specimen contains antibodies that react with the antigens immobilized on the nitrocellulose membrane, a reddish-purple line appears, qualitatively indicating the presence of antibodies to HIV-1, HIV-2, or both in the specimen.

Also CLIA-waived for its simplicity, Uni-Gold involves obtaining a blood specimen from a finger prick, adding 1 drop to the test device, adding 4 drops of wash solution, and waiting 10 minutes for the result. According to Trinity's device description, it was designed as a rapid immunoassay based on the immunochromatographic sandwich principle. The assay employs genetically engineered recombinant proteins representing the immunodominant regions of the envelope proteins of HIV-1.

"The recombinant proteins are immobilised at the test region of the nitrocellulose strip," according to the description submitted to the FDA. "These proteins are also linked to colloidal gold and impregnated below the test region of the device. A narrow band of the nitrocellulose membrane is also sensitized as a control region. If antibodies to HIV-1 are present in the sample, they combine with an HIV-1 antigen/colloidal gold reagent and this complex subsequently binds to the immobilized antigens in the test region of the device forming a visible pink/red band." Both the Uni-Gold and OraQuick tests have built-in controls and can be stored at room temperature.

Among the non-CLIA waived tests, Reveal requires reconstituted and refrigerated reagents. Preparation involves using a centrifuge to obtain serum or plasma, adding a buffer to reconstitute the conjugate, adding 3 drops of buffer to moisten the membrane, 1 drop of serum or plasma, 3 more drops of buffer, 4 drops of a detection agent, and 3 more drops of buffer to wash, at which time the results can be read. Time to result is 5 minutes. Multispot also requires refrigerated reagents. It is a 15-minute test that begins by diluting plasma or serum and removing and discarding a pre-filter. Several timed reagents and wash steps follow, after which test results can be read.

According to the CDC's Division of HIV/AIDS Prevention, non-reactive results from rapid HIV tests are considered negative, but if the person being tested was exposed to HIV within the prior 3 months, a repeat test at a later time is recommended. Reactive results are considered preliminary positive and must be confirmed by Western blot or immunofluorescence assay (IFA).

Where They Work

Rapid tests for HIV antibody are considered most useful in obstetric wards, healthcare worker occupational exposures, urgent care clinics and emergency departments, military medicine, public health settings, developing countries, and primary care offices, according to Keenan and colleagues. In obstetric wards, the CDC recommends routine, rapid HIV testing of women in labor when their HIV status is unknown, as well as testing of a newborn if the mother's status is unknown at delivery. Results from the CDC-funded Mother-Infant Rapid Intervention at Delivery (MIRIAD) study show that rapid testing under these circumstances is both feasible and useful in reducing mother-to-child transmission of HIV through the timely delivery of antiretroviral medication.

Among health care workers exposed to HIV on the job, prompt treatment can decrease the subsequent risk of HIV infection by more than 80%, but treatment should begin within 1 to 2 hours after exposure. Tests delivering results in up to 20 minutes, as opposed to 3 to 4 days, facilitate successful treatment. Similarly, rapid tests in emergency rooms and military settings facilitate timely treatment.

In developing countries, rapid tests are making possible radical scaling up of HIV testing and counseling services as called for by the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) in their "Treat 3 Million by 2005" initiative. "The use of rapid HIV tests will facilitate this in many settings, particularly in services where those most likely to benefit from knowledge of their HIV status can be reached, [eg, for the diagnosis and treatment of tuberculosis (TB) and sexually transmitted infections (STIs)], in services providing and linked to the prevention of mother-to-child transmission, and in general medical settings," according to WHO's 2004 report, *Rapid HIV Tests: Guidelines for Use in HIV Testing and Counselling Services in Resource-Constrained Settings*.

Rapid testing offers an affordable alternative that is increasing the number of people tested worldwide, as well as the number of people who find out their test results. The CDC and the World Health Organization (WHO) have developed testing algorithms involving a series of 2 or 3 rapid tests, which can confirm HIV test results as reliably as Western blot. Referral laboratories would be used when confirmatory results are inconclusive.

"Because screening with combinations of rapid HIV tests is much less expensive than using the EIA-Western blot algorithm, rapid tests can facilitate the expansion of VCT (voluntary counseling and testing) services in both urban and rural sites," wrote Branson in "Point of Care Rapid Tests for HIV Antibody" in the *Journal of Laboratory Medicine* in 2003.

Pre- and post-test counseling are considered critical to reducing the risk of infection and the spread of HIV, and to getting proper treatment. "HIV testing and counselling have been recognized as necessarily linked since the first HIV enzyme-linked immunosorbent assay (ELISA) tests became available for the identification of HIV infection in the mid-1980s," the 2004 WHO report states. "The linkages between the testing and counseling service and the health care facility are extremely important for further prevention and care of people living with HIV/AIDS and their families." With rapid tests for HIV, counseling includes information about the importance of HIV testing; ways to reduce the risk of becoming infected with HIV; next steps for people who have a reactive test result; and the need for additional testing in people who have had a recent exposure to HIV. LM