

II. DEVELOPMENT OF RAPID HIV TESTS

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Topic: Rapid HIV Tests intended for use as an aid in diagnosis in outreach, public health, hospital and clinical settings.

Background:

Introduction

Several manufacturers are at various stages of developing and bringing to the US market rapid HIV tests exclusively intended for use as an aid in diagnosis (not for blood screening). These HIV rapid tests provide a quick (less than 20 minute) result for detection of HIV antibody, based on immunoassay techniques. The tests are intended for use in clinical settings (emergency rooms, hospital clinics), public health settings (sexually transmitted disease clinics, family planning clinics), and outreach settings (HIV outreach sites) where obtaining HIV test results during a single visit would be beneficial. Rapid HIV tests may be used to provide a preliminary result for detection of antibody to HIV prior to confirmation by supplemental western blot testing when the rapid test result is positive. The tests offer a rapid and simple alternative to licensed enzyme-linked immunosorbent assay (ELISA) products that are technically complicated, take hours to perform, and require specialized equipment.

These rapid HIV tests intended for diagnostic use, not for blood screening, are regulated as class III devices. Responsibility for assuring the safety and effectiveness of these kits lies within the Center for Biologics Evaluation and Research's Office of Blood Research and Review, with oversight by the Blood Products Advisory Committee (BPAC). The tests should meet the regulations in the 21 CFR 800 series subparts, under the Investigational Device exemption (IDE) and Pre Market Approval (PMA) pathways. This pathway represents a digression from the usual purview of BPAC, which primarily considers policy and products that directly impact blood safety and are typically regulated in the 21 CFR 600 subparts. However, providing oversight for products intended as an aid in diagnosis of HIV under the IDE/PMA pathway is not new to BPAC (e.g., the oral sample collection device and the HIV home collection test have been brought to BPAC and approved as PMAs).

This session on rapid HIV tests intended for use as an aid in diagnosis in outreach, public health, hospital and clinical settings has several goals. The primary goal is to provide the committee with an update on the status of rapid HIV tests in the US, to include a review of data indicating the potentially strong public health benefit of having multiple rapid HIV tests available in the USA, as well as preliminary performance data for rapid tests in US populations. Another goal is to introduce the concept of an alternative algorithm, using a combination of rapid HIV tests, for providing statistically validated HIV serostatus results to an individual in lieu of confirmation by a supplemental test. The final goal is to gain committee concurrence on FDA's approach to setting approval standards for these assays and to handling a novel algorithm for determining HIV serostatus based exclusively on rapid tests.

What is a rapid HIV test?

A rapid HIV test provides a result that indicates the presence or absence of antibodies to HIV within 20 minutes (usually less than 10 minutes). These tests are designed to be rapidly performed and interpreted by a trained individual on-the-spot (at the site the sample is taken). The tests are provided as kits with all reagents included, need no specialized equipment, and in some cases do not require refrigeration. The result is based on visual detection of an HIV-specific spot or line (usually pink or blue in color); most assays include a "control" spot or line to indicate proper performance of kit components.

How do rapid HIV tests work?

Although there are different formats for rapid tests, two formats are the primary focus of development efforts: flow through membrane immunoconcentration devices and lateral flow immunochromatographic strips. In both of these types of tests, the specific antibody reactivity is achieved by placement of HIV-specific antigens onto a membrane. The flow through membrane immunoconcentration device is a cassette that holds a permeable membrane onto which HIV antigens have been placed in spots or strips. This device requires multiple steps after addition of sample, including wash steps and sequential additions of conjugate and color development reagents. In this type of kit, when the sample flows through the antigen on the membrane, HIV antibodies (if present in the sample) interact with the antigen. After nonspecific associations are cleared away by washing, the conjugate will attach to the antibodies captured on the membrane, and then this conjugate will cause a color reaction with the substrate during the last steps of the assay. A positive reaction would be visible as a spot or line of color on the membrane (color would depend upon the substrate used). Most of the assays include a "control" spot or stripe that indicates that sample has been added and that, depending on the design of the particular kit, the kit components are performing properly. Some flow through kits require refrigeration of reagents.

Lateral flow immunochromatographic strips usually involve one or two steps. Sample may be added directly to the strip or may be diluted before being added. The liquid from the sample flows along the surface of the strip, after mixing with detection reagents (e.g., colloidal gold) embedded in the sample pad. When the sample passes over the HIV antigen affixed to the strip, HIV antibodies (if present) in the sample interact with and attach to the antigens, causing the gold to collect and creating a visible band. All of these assays include a "control" stripe which the migrating sample front flows across after it has passed the HIV antigen stripe. This control line indicates that sample has been added and that the kit components are performing properly. These kits usually do not require refrigeration of reagents.

What rapid tests are available in the US?

Two rapid HIV assays were licensed for use in the US, the Cambridge Biotech Corp. Recombigen HIV-1 Latex Agglutination assay, licensed in 1989, and the Abbott/Murex Diagnostics, Inc. SUDS HIV-1 Test, licensed in 1992. Both of these rapid assays were licensed as screening tests (including use in blood banks under restricted conditions) for the rapid detection of antibodies to HIV-1 in plasma or serum. The Recombigen LA Assay has been withdrawn from the market, leaving the SUDS test as the single HIV rapid test currently approved by the FDA for use in the US. This test was licensed with a screening claim limited to use in settings where microwell enzyme immunoassays are not practical or available. This single test availability is in contrast to other parts of the world (some members of the European community and nations in Africa) where many rapid HIV assays are on the market. These rapid HIV tests have been fulfilling a need for making HIV testing available in situations where there is limited equipment and refrigeration.

Why more rapid tests are needed in the US.

The present algorithm for providing test results is to perform an initial licensed screening test followed by a licensed western blot for samples that are repeatedly reactive on the screening test. In current practice, because testing is primarily conducted in batches at centralized testing laboratories, it takes from 24 hours to 2 weeks to deliver results. In the past few years, studies have demonstrated that in some settings there is a need to eliminate this delay. There is a need in diagnostic settings to provide same visit results to individuals seeking testing because an estimated 8,000 HIV positive individuals do not return to receive their results each year (1998 MMWR). There is also a need to provide rapid HIV serostatus results for pregnant women at risk for HIV infection, presenting for delivery with unknown HIV serostatus. Studies have shown that antiviral therapy initiated during labor to previously untreated mothers or initiated to neonates during the first 48 hours after birth can reduce the incidence of HIV transmission to the infants by half (Guay et al., 1999; Wade, et al., 1998). The studies which point to the urgency of these and other needs will be described in more detail by representatives from CDC and NYC DOH during the session.

The settings in which there is a need for rapid HIV tests present several challenges. In order to be useful in these settings, the rapid HIV tests must be extremely simple to perform, the sample specimen should be easy to obtain (in some instances venipuncture is not practical or available), and the tests should demonstrate appropriate sensitivity and specificity in their targeted populations (usually individuals at risk for exposure to HIV infection). The currently licensed rapid HIV test is moderately complex to perform (according to The Clinical Laboratory Improvement Act) and requires properly trained personnel to carry out the test. In some settings, because of prevailing state, local or clinical practices or standards, this means the test must be performed in a clinical laboratory, causing a significant time delay for the sample to be sent, test performed and results relayed back.

How may rapid HIV tests be used?

The rapid HIV tests may be used in non donor settings to provide a preliminary result to an individual during the initial visit for testing. Individuals with samples testing negative would be counseled that they are negative for HIV antibodies. Individuals testing positive would be counseled that they have an initial positive result that should be confirmed by supplemental testing. In order to receive confirmation of serostatus, the individual will have to return to receive results from the confirmatory testing. The rapid tests would offer the advantage of identifying negative individuals and letting positive individuals know they may be positive during their first visit so that secondary infections may be avoided.

In addition to being used individually, in some countries rapid HIV tests are being used in multi-test algorithms to improve the predictive value of the combined result. These algorithms fit the three strategies for HIV testing recommended by the World Health Organization (Weekly Epidemiological Record 1997). The multi-test algorithms have been under investigation and in use in Africa for several years. Three rapid tests used in dual test combinations achieved 100% sensitivity and specificity in field trials in low prevalence (1.5%) populations in Honduras (Stetler et al., 1997). In these same trials the positive predictive value (PPV) was 100% and the negative predictive value ranged from 99.3% to 99.6% for a high prevalence population (30.5%). In a dual test algorithm conducted in Cote d'Ivoire, the combined study PPV was 99.6% and the NPV was 99.9% (Brattegard et al., 1993). Another dual rapid test algorithm yielded 100% sensitivity and specificity at a cost 6 to 9 times less than the standard algorithm (van der Groen, 1991). A different dual test algorithm achieved 99.9% specificity (with a sacrifice of sensitivity to 96.9%) in Nigeria (Kline, et al., 1994). More recently, an evaluation of three rapid HIV tests in Uganda identified a multi-test algorithm that provided 100% sensitivity and specificity for 325 individuals, who received results and completed counseling in less than 2 hours (Downing, et al., 1998). The predictive values delivered by multi-test algorithms were affected by the HIV prevalence in the population tested, the choice of the tests used in the algorithm, and the choice of decision rules (e.g., one rule might be that all test results must be positive in order for the combined result to be positive, an alternative rule might be that a single positive result is sufficient for the combined result to be positive). The choice of tests and decision rules may be targeted toward desirable predictive values for the populations served at specific test sites. Multi-test algorithms are being evaluated in US populations under the auspices of the CDC, which is in the early phases of a study to determine the performance of rapid HIV tests individually and in combination to provide a statistically validated result as a rapid alternative to supplemental testing.

What FDA is doing to accommodate the need for rapid HIV tests.

The public health interests for rapid HIV tests have differences from those for blood donor screening HIV tests. While continuing to assure safety and effectiveness of the assays, FDA is taking steps to facilitate approval of rapid tests. During the March 25, 1999 BPAC session, FDA postponed the requirement for inclusion of group O antigens for rapid tests (approvals of all tests will include a postmarket commitment from the manufacturer to amend their application file with their proposal for adding group O antigens within two years). In addition, FDA has reduced the number of samples needed for a statistically significant determination of specificity of the tests (from 10,000 to 6,000) and will be revisiting the sample sizes needed to demonstrate performance of the tests.

Recognizing that rapid HIV tests will be used to meet public health needs different from those met by the blood screening HIV tests, FDA is proposing to apply a separate standard for approval of rapid HIV tests. FDA's position is outlined below.

FDA Position: Criteria for Approval of a Rapid Test for HIV-1 Antibody for Serum/Plasma

Sensitivity:

1. 100% sensitivity (currently 11 out of 11) on the FDA HIV-1 Lot Release Panel.
2. Minimum standard of performance in the clinical trials:

The tests should meet a standard representing current state of the art based on rapid test data for fresh samples from US populations for Western blot positive serum/plasma samples from known HIV-1 infected individuals and from infected individuals tested as part of a high risk population. The standard is the lower bound of the 95% confidence interval for all positives from the combined studies of known positives and prospectively tested high risk individuals. The sample sizes that FDA currently requests are 1000 known positives and 500 individuals of unknown serostatus. Based on these sample sizes and state of the art data, the standard is 98%. That is, the lower bound for the 95% confidence interval for known and confirmed positives must be at least 98%.

Specificity:

1. Minimum standard of performance in the clinical trials:

The tests should meet a standard representing current state of the art rapid test data for fresh samples from US populations in a low risk population(s). The standard is the lower bound of the 95% confidence interval for the low risk sample sizes that FDA currently requests (6,000). Based on this sample size and state of the art data, the standard is 98%. That is, the lower bound for the 95% confidence interval for low risk studies must be at least 98%.

FDA Position: Labeling of Rapid Tests

FDA is proposing to review and label rapid tests on an individual basis. Kits providing data sufficient for approval in their own right as a medical diagnostic test for the presence of antibodies to HIV (e.g., _____) will be approved individually. Manufacturers must provide data sufficient to define sensitivity and specificity of the assay in intended use populations, as well as evidence of consistent manufacturing and test reproducibility. Labeling will follow current practice, e.g., "for use as an aid in diagnosis."

When tests are approved they may be used in a multi-test algorithm to improve the predictive value of the combined result. The labeling may also indicate that "this test may be used as part of a multiple test algorithm to obtain statistical validation of the test result in settings where the use of an approved supplemental test for HIV antibodies is impractical or not feasible prior to patient counseling."

Questions for the Committee:

1. Does the Committee agree with the FDA criteria for approval of a rapid test for use in a diagnostic setting?
2. Does the Committee agree with the FDA approach to labeling rapid tests?

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Speaker – Kimber Poffenberger, Ph.D.

Listed Reprints

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2. *Weekly Epidemiological Record*, 1997, 72, pp.81-88, World Health Organization, Geneva.
3. Stetler, Harrison C., Granade, Timothy C., Nunez, Cesar A., et al. Field Evaluation of Rapid HIV Serologic Tests for Screening and Confirming HIV-1 Infection in Honduras, *AIDS* 1997, 11:369-375.
4. Kline, Richard L., Dada, Abinbola, Blatner, William; Quinn, Thomas C., Diagnosis and Differentiation of HIV-1 and HIV-2 Infection by Two Rapid Assays in Nigeria, *Journal of Acquired Immune Deficiency Syndrome*, Vol. 7, No. 6, 1994.
5. Brattegaard, Kari; Douoadio, Justin; Adom, Marie-Laure, et al. Rapid and Simple Screening and Supplemental Testing for HIV-1 and HIV-2 Infections in West Africa, *AIDS* 1993, 7:883-885.
6. Vander Groen, G; Van Kerckhoven, I.; Vercauteren, G.; Piot, P. Simplified and Less Expensive Confirmatory HIV Testing., *WHO Bulletin OMS*, Vol. 69 (6): 747-752, 1991.
7. Downing, Robert G.; Otten, Ron A.; Marum, Elizabeth; et al. Optimizing the Delivery of HIV Counseling and Testing Services: The Uganda Experience Using Rapid HIV Antibody Test Algorithms, *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 18:384-388, 1998. (No copy of article #7 provided)