Point-of-Care Rapid Tests for HIV Antibodies

Patientennahe Schnelltests für den Nachweis von HIV-Antikörpern

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Summary: Rapid tests to detect HIV antibodies have been widely used over the past decade. Many simple, rapid HIV tests demonstrate sensitivities and specificities comparable to those of enzyme immunoassays (EIAs) without the need for sophisticated laboratory equipment and highly-trained technicians. Algorithms comprised of two or more rapid tests can also produce HIV test results as accurate as the EIA-Western blot combination. Rapid assays that can be used with whole blood or oral fluid specimens have now been developed and make point-of-care (POC) HIV testing feasible. POC tests can make HIV testing accessible in areas with limited laboratory facilities and greatly reduce the number of persons who do not learn their test results. POC testing can also provide immediate test results that are needed to make decisions about antiretroviral prophylaxis for pregnant women in labor and for health care workers who have had occupational exposures to blood or body fluids. This review summarizes available data on the characteristics and performance of individual HIV rapid tests from independent evaluations, peer-reviewed journals, and conference abstracts and describes experiences with the POC use of rapid HIV tests for voluntary counseling and testing (VCT) and perinatal screening.

Keywords: HIV antibody testing; rapid serological assays; point-of-care testing; alternative confirmatory strategies.

Zusammenfassung: Schnelle Tests für den Nachweis von HIV-Antikörpern werden häufig eingesetzt. Viele einfache und schnelle HIV-Tests haben eine Sensitivität und Spezifität, die vergleichbar ist mit denen von Enzymimmunoassays (EIAs), ohne die Notwendigkeit von ausgeklügelten Laborgeräten und starkausgebildeten Laboranten zu haben. Die kombinierte Information von zwei oder mehr Schnelltests kann HIV-Testresultate ergeben, die so sicher sind wie die EIA-Western-blot-Kombination. Es wurden Schnelltests für die Untersuchung von Vollblutproben oder Mundflüssigkeit entwickelt, sodass point-of-care (POC) HIV-Testung machbar ist. POC-Tests erlauben die HIV-Testung in Bereichen mit begrenzter Verfügbarkeit von Laboratorien und können somit die Zahl von Personen mit unbekanntem HIV-Infektionsstatus reduzieren helfen. POC-Testung kann zudem sofortige Testergebnisse erzeugen, die notwendig sind, um Entscheidungen über antiretrovirale Prophylaxe bei entbindenden Frauen oder bei im Gesundheitswesen Tätigen zu fällen, die Blut oder anderen Körperflüssigkeiten exponiert wurden. Diese Übersichtsarbeit fasst die verfügbaren Informationen über die Characteristika und Leistung von verschiedenen HIV-Schnelltests aus unabhängigen Evaluationen, peer-reviewed Fachzeitschriften, und Kongressabstracts zusammen und beschreibt Erfahrungen mit dem POC-Einsatz von HIV-Schnelltests bei der Beratung und Testung von Freiwilligen und dem perinatalen Screening.

Schlüsselwörter: HIV-Antikörper-Testung; Schnelltest; Point-of-Care Testung.

Antibody testing for human immunodeficiency virus (HIV) began in 1985 with the introduction of the enzyme immunoassay (EIA) for the screening of donated blood. The traditional platform for HIV testing was thus designed to meet the need to protect the blood supply: tests with high sensitivity, suitable for batch processing of high volumes of specimens in centralized laboratories with specialized equipment. Voluntary counseling and testing (VCT) services were soon established to offer HIV antibody testing as a means for high-risk persons to determine their HIV status. Concerns about false-positive results from the use of screening tests in low-prevalence populations [1] led to the implementation of a sequential two-test algorithm: screening with an EIA followed by Western blot as a supplemental test to confirm HIV positivity [2]. The US Public Health Service recommended that no positive test results should be given to patients until the screening test had been repeatedly reactive on the same specimen and the supplemental test had been used to

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validate those results [3]. In practice, given the time necessary to transport specimens to a laboratory, perform the tests in batches, and transmit test results, tested persons typically must wait 1–2 weeks before they make a second visit to learn their test results.

The EIA and Western blot became the "gold standard" for detection of HIV antibodies. However, these tests have several disadvantages. EIAs are technically demanding and require sophisticated, regularly maintained equipment (automatic pipettes, incubators, washers, and readers), and a constant electricity supply. This is not feasible for many developing countries where resources are limited and electricity may not be consistently available [4]. Efficient use of EIA tests also requires a minimum number of specimens per run, corresponding to the 96-well microtiter plate set-up. Small laboratories thus may delay testing until a sufficient number of specimens accumulate. Disadvantages of the Western blot include its high cost, the need for well-trained technicians, lack of consensus in the interpretation criteria, and the occurrence of indeterminate results [5].

For testing to be effective as well as accurate, HIV test results must be available within as short a period of time as possible. When testing is done in centralized laboratories, turnaround times range from several days in developed countries to several months for specimens sent from rural areas in developing countries [6, 7]. Up to 50 % of persons testing in VCT and antenatal clinics, including many who are HIV-positive, do not return to collect their results and thus much of the benefit of testing is lost [8–13]. Availability of same-day test results increases both acceptance of voluntary testing [14, 15] and receipt of results [11, 12, 16–18]. Depending on the setting, even relatively small delays can affect the number of persons who learn their test results. In one study of rapid HIV tests, 55 % of patients in an emergency department left before receiving their test results when the mean turnaround time for testing was 107 minutes, compared with 20 % when mean turnaround time was 48 minutes [19].

The evolution in diagnostic technology has led to the development of a wide range of simple, rapid HIV assays. Many were designed to be performed in laboratories with serum specimens [20–31]. Studies demonstrated that alternative confirmatory algorithms based on combinations of screening tests produced results comparable to those of the standard EIA-Western blot algorithm [6, 32–36]. In 1992, the Global Programme on AIDS and World Health Organization (WHO) first recommended the use of testing strategies based on combinations of screening tests (including simple, rapid tests) for blood screening, surveillance, and diagnosis in place of the EIA and Western blot [37]. These recommendations were revised as the range of available antibody tests expanded (Table 1), but were still intended for testing of serum or plasma [38]. Because screening with combinations of rapid HIV tests is much less expensive than using the EIA-Western blot algorithm [6, 35], rapid tests can facilitate the expansion of VCT services in both urban and rural sites and into antenatal services where the demand for VCT is likely to rise with the development of interventions to prevent mother-to-child transmission of HIV [39]. Both providers and clients prefer rapid tests over traditional testing [34, 40]. Because of the potential for rapid tests to increase the number of people who learn their HIV test results, in 1998 the US Public Health Service recommended that practitioners should provide preliminary results from rapid HIV tests before confirmatory results are available in situations where tested persons benefit [41].

Table 1 UNAIDS/WHO recommendations for HIV testing strategies [38]

Objective	Prevalence	Strategy
Blood Screening	All	1
Surveillance	> 10 %	1
	≤ 10 %	2
Diagnosis Signs/symptoms	> 30 %	1
	≤ 30 %	2
Diagnosis Asymptomatic	> 10 %	2
	≤ 10 %	3

Strategy 1: Single screening assay. Reactive test is considered positive.

Strategy 2: Two screening assays. If initial test is reactive, test is repeated with second assay. Specimen considered positive only when both assays are reactive.

Strategy 3: Three screening assays. Specimen considered positive only when all three assays are reactive.

The most recent development – rapid tests that can detect HIV antibodies in whole blood specimens [42–46] – makes it possible to conduct true point-of-care (POC) HIV testing. The specimen requires no processing, so the need for equipment (such as a centrifuge) and electricity is eliminated. Because the procedures are very easy, involve a limited number of steps, and do not require high precision, they can be carried out outside traditional laboratory settings by staff with no formal laboratory training [39].

Assay formats

Most rapid assays are in kit form that include all necessary reagents and require no other specialized equipment. The three most common assay formats that can be used with whole blood are particle agglutination, immunoconcentration, and immunochromatograpy. Particle agglutination assays typically require 10 to 60 minutes or more. When a patient specimen containing

HIV antibodies is mixed with latex particles coated with HIV antigen, cross-linking occurs and results in agglutination. Results are interpreted visually. Because detection of weak agglutination can be difficult, readers have been developed for some tests to reduce the inaccuracy introduced by subjective interpretation. Although most are used with serum or plasma, some have been developed for use with whole blood. The reagents often require refrigeration, and costs range from US$ 2 to $ 4 per test.

Immunoconcentration (flow through) devices employ solid-phase capture technology, which involves the immobilization of HIV antigens on a porous membrane. The specimen flows through the membrane and is absorbed into an absorbent pad. A dot or a line visibly forms on the membrane when developed with a signal reagent (usually a colloidal gold or selenium conjugate). Some tests allow the differentiation of HIV-1 from HIV-2 by applying antigens from these viruses to different sites on the membrane. The flow-through tests usually require several steps for the addition of specimen, wash buffers, and signal reagent. They can usually be performed in 5 to 15 minutes. Several immunoconcentration devices include a procedural control on the membrane; the appearance of a colored dot or line at this location confirms the test has been performed correctly. Many flow-through tests are designed for use only with serum or plasma. Some are equipped with a filter or include an initial dilution step with lysis of red blood cells that allows the use of whole-blood specimens. The devices or reagents typically require refrigeration. Costs range from US$ 4 to $ 12 per test.

Immunochromatographic (lateral flow) strips, the most recent development, incorporate both antigen and signal reagent into a nitrocellulose strip. Many lateral flow tests require only a single step. The specimen (usually followed by a buffer) is applied to an absorbent pad. Alternatively, the specimen is diluted in a vial of buffer, into which the test device is inserted. The specimen migrates through the strip and combines with the signal reagent. A positive reaction results in a visual line on the membrane where HIV antigen has been applied. A procedural control line is usually applied to the strip beyond the HIV-antigen line. A visual line at both the test and control sites indicates a positive test result, a line only at the control location indicates a negative test result, and the absence of a line at the control site means the test is invalid. Some tests apply HIV-1 and HIV-2 antigens in different locations and allow differentiation of antibodies to these two viruses. Most lateral-flow tests require no additional equipment or refrigeration, and test results can be obtained in 20 minutes or less. Many can be used with whole blood, serum, or plasma, and some can be used with finger-stick blood specimens, saliva or oral fluids. In most lateral-flow devices, the test strip is encased in a plastic cartridge. Cost of these tests is usually less than US$ 10.

Test performance

Methods of antigen production (viral lysate, synthetic peptide, recombinant peptide) and specific combinations of antigens differ with each individual assay. Most include one or more antigens from the viral envelope of HIV-1 (gp41, gp120, gp160) and HIV-2 (gp 36); some also incorporate core antigen (p24). No central standards body evaluates the accuracy of rapid HIV tests. Because regulatory requirements and approvals in many countries are often minimal compared with those established by the US Food and Drug Administration (FDA), it can be difficult to compare the sensitivity and specificity of different tests with confidence. Devices are sometimes made by one company but distributed and sold under several brand names, which leads to confusion and makes it difficult to compile a comprehensive list. WHO, through its Department of Blood Safety and Clinical Technology, periodically evaluates EIAs and rapid tests that are available for bulk purchase by the public sector. These evaluations are done voluntarily, usually at the request of the manufacturer. The tests are performed on a panel of approximately 600 sera of diverse geographic origins and on seroconversion panels [47]. Results of these evaluations are available via the internet at http://www.who.int/bct. To serve the needs of blood transfusion services, which use the vast majority of HIV tests worldwide, increasingly sensitive assays have proliferated. As a result, many less sensitive but highly specific assays have been withdrawn from the market [39]. Table 2 describes commercially available tests for which performance data are available from the WHO or other published independent evaluations.

Systematic evaluations of rapid HIV tests with non-B subtypes of HIV-1 group M, group O, and HIV-2 have established that most tests adequately detect all subtypes of group M, but performance is more variable with group O and HIV-2 strains [48–51]. Some tests include only HIV-1 antigens and detect only those HIV-2 strains with cross-reacting epitopes; others reliably detect HIV-2 antibodies, and some differentiate HIV-1 from HIV-2. Performance with group O strains is similar to that of EIAs currently in use. Data from seroconversion panels demonstrate the analytic sensitivity of many newer rapid assays to be comparable to that of whole-viral lysate EIAs [35, 47, 52], but they detect antibodies 2–8 days later than third-generation EIAs [50].

Although more than 60 rapid HIV tests have been developed and used in various countries, few are in use in developed countries, and only 3 have received approval from the FDA for use in the United States. The first, Recombigen HIV-1 LA [53], was a latex agglutination test. As is true for many other agglutination tests, even technicians with extensive training had difficulty distinguishing reactive test results from the background granularity of the latex particles [26]. Recombigen was later withdrawn from the U.S. market because of poor per-

Table 2 Performance characteristics of commercially available rapid point-of-care HIV tests

Manufacturer	Product	Principle	Sensitivity %	Specificity %
Abbott Laboratories Abbott Park, Illinois USA	Determine HIV-1/2/O	LF	100	99.4
	SUDS HIV-1	FT	99.8	75.1
AccuDx Inc. San Diego, California USA	AccuSpot HIV-1 and HIV-2	FT	100	86.3
BioRad Laboratories Redmond, Washington USA	Genie II HIV-1/2	FT/LF	99.8	100
	Multispot HIV-1/2	FT	99.6	99.8
Chembio, Inc. Medford, New York USA	FastCheck HIV1/2	LF	99.6	99.8
Efoora. Inc. Chicago, Illinois USA	Efoora HIV 1/2/O	LF	99.6	99.9
Embee Diagnostics Delhi, India	HIV Tri-Dot	FT	99.6	99.7
Fujirebio Tokyo, Japan	Serodia HIV-1/2	PA	100	98
Genelabs Diagnostics Singapore	HIV-Spot	FT	98.2	99.7
Guardian Scientific Africa Monmouth Beach, New Jersey USA	Quix HIV-1/2/O	FT	100	99.8
InTec Products, Inc. Xiamen, China	Advanced Quality Rapid HIV Test	LF	98.8	100
Merlin Biomedical and Pharmaceutical Huntington Beach, California USA	Merlin Immediate HIV-1 and HIV-2 test	LF	99.8	100
MedMira Laboratories Halifax, Canada	Med Mira HIV 1/2	FT	100	97.6
OraSure Technologies Inc. Bethlehem Pennsylvania USA	OraQuick Rapid HIV Antibody Test	LF	99.6	100
Orogencis Ltd. Yavne, Israel	DoubleCheck HIV-1/2	FT	100	99.7
Ortho Diagnostics New Brunswick, New Jersey USA	HIVCHEK System 3	FT	99.6	99.7
PMC Medical Pty. Ltd. Daman, India	First Response HIV-1/ HIV-2 WB	LF	100	98.8
Saliva Diagnostic Systems New York, New York USA	Hema-Strip HIV-1/2	LF	99.6	99.9
	Sero-Strip HIV-1/2	LF	98.9	100
Span Diagnostics Surat, India	CombAIDS RS	FT	100	88
Trinity Biotech plc Bray, Ireland	Capillus HIV-1/2	PA	100	100
	SeroCard HIV-1/2	FT	100	97.9
	UniGold Recombinant HIV-1/2	LF	100	100
Wiener Laboratorios Rosario, Argentina	DIA HIV-1+2	FT	99.6	99.4

Notes to table: FT = flow-through; LF= lateral flow; PA = particle agglutination. Sensitivity and specificity represent published reports against multiple HIV-1/2 subtypes from independent evaluations.

formance. SUDS (Single Use Diagnostic System for HIV-1) is a flow-through test approved in 1992. Because reagents require refrigeration, its procedure involves multiple steps, and the test has no internal control, SUDS is not well-suited for POC use. In November 2002, the FDA approved the OraQuick test for use with finger stick whole blood [46] and soon thereafter categorized the test as waived under the Clinical Laboratory Improvement Amendments (CLIA). This category involves the least stringent regulatory

oversight, and paves the way for its POC use outside of traditional laboratory settings. In Canada, two tests were approved for POC use by health professionals in March 2000: the Fastcheck HIV 1/2 and MedMira HIV 1/2 tests [54].

Assessing the accuracy of POC tests poses a challenge. Most rapid tests have been evaluated with serum specimens, but their accuracy with whole blood may not be equivalent [55]. The WHO has recently undertaken assessments with whole blood [56], but because whole blood deteriorates with storage, it cannot be used for further testing at a later date and it will not be possible to compare different tests with the same specimens. The ability to generate accurate POC results depends not only on the intrinsic quality of the test itself but also on extrinsic qualities such as the skills of the performer and quality of the specimen. Visual interpretation of results is subjective, and published assessments of particle agglutination tests document inter-reader variability ranging from 3 % to 10 %, especially with weakly positive specimens [23, 57]. In the WHO evaluations, inter-reader variability was less than 2 % with most lateral flow tests that included an internal procedural control, but 10 % to 23 % for flow-through tests with no internal control [47].

Algorithms for confirmation

The initial test used for HIV screening should have the highest possible sensitivity and an internal procedural control to indicate the test has been performed correctly. With a sensitive screening test, the predictive value of a negative test result is high, and specimens non-reactive on the screening test are considered HIV-antibody negative [38]. However, because the predictive value of a positive test varies with the prevalence of HIV infection in the population tested, the positive predictive value of a test will be low in populations with low prevalence. Thus, all reactive screening tests require confirmation. Many developed countries continue to use the Western blot to confirm reactive POC rapid tests [46, 54]. The alternative confirmatory strategy currently advocated by the WHO requires three assays based on different principles or antigens [38]. In practice, it can be difficult to ascertain which specific antigens are present in a given test. The WHO and Joint United Nations Programme on AIDS developed guidelines for in-country evaluations for the selection of rapid HIV tests for use in combination algorithms [58]. The overall accuracy of the testing algorithm depends on the characteristics of the specific tests, the order in which the tests are used, and on the rules for resolving discordant results [59]. The second and third tests in the algorithm should be selected on the basis of high specificity. The number of initial discordant results from the first two tests should not exceed 5 % [38]. If it does, quality assurance procedures should be checked, or a new test combination should be adopted. However, confirmatory algorithms based on combinations of screening tests can be difficult to validate. Many published studies of confirmatory strategies use a combination of two sensitive EIAs as the standard for comparison. Evaluations that compare results to the Western blot often exclude indeterminate specimens. This approach can overestimate the specificity of individual tests [36].

Discussion

Test sensitivity and specificity alone are not sufficient to establish optimal paradigms for HIV screening. Both logistics and economics pose significant challenges to accomplish the main objectives of HIV antibody testing. POC rapid tests have been most widely implemented in African countries hard-hit by the HIV epidemic. Their experiences are not yet well documented in the literature but were described during a symposium at the 2002 World AIDS conference in Barcelona, Spain. The provision of same-day test results greatly increased the demand for VCT. The number of clients testing at one VCT site in Malawi increased from 5,000 to more than 40,000 annually within a year after the introduction of rapid tests [60]. The proportion of those tested who learned their results also increased from 69 % to 99.7 %. The use of whole blood tests allowed extension of VCT into both urban and rural sites with no laboratories. In Kenya, VCT services were expanded from 3 sites to more than 70 locations. Counselors perform the tests during the counseling session and allow clients to see their test strips and participate in the interpretation of results. This was reported to increase clients' confidence, because they can be certain that the test was performed, and that no mix-up occurred as might happen with transport of specimens. Parallel testing of duplicate specimens documented that rapid test results were accurate, equal to or exceeding that of testing performed in the hospital laboratory [60]. In a large trial that included 3800 patients in field settings in Zimbabwe, two lateral flow tests (Determine and Unigold Recombinant) performed by trained nurse counselors demonstrated excellent sensitivity and specificity, whether or not testing was supervised by a laboratory technologist [61].

For several reasons, the expanded use of POC rapid HIV antibody tests promises to play an important role in HIV prevention both in developed and developing countries. First, antiretroviral therapy reduces vertical transmission when used intra- or postpartum [62, 63]. Despite expanded prenatal HIV screening programs, many pregnant women are not tested before delivery, and HIV prevalence is often substantially higher among women who do not receive prenatal care [64, 65]. Access to immediate HIV test results could improve the judicious application of prophylactic regimens [66–68]. Results of POC testing done in the labor and delivery suite are available in less than half the time as when the same tests are done in the laboratory [69]. In labor and

delivery, delays of even one hour or less may determine whether or not therapy can be initiated intrapartum. Second, antiretroviral therapy reduces occupational HIV transmission when started as soon as possible after percutaneous exposures [70]. POC rapid tests facilitate the rapid and accurate evaluation of source patients, considerably reduce anxiety and adverse effects for the health care worker from unnecessary antiretroviral agents, and result in substantial cost savings [71, 72]. Third, HIV infection in many persons who seek health care services remains undiagnosed [73–75]. POC tests make it feasible to routinely offer HIV testing in health care settings. Finally, several studies indicate that persons who are aware they are HIV-infected adopt behaviors that make their transmission of HIV infection less likely [76–78]. POC rapid tests can substantially increase the number of persons who are tested and who receive their test results [11, 17, 18, 34]. Persons who are aware of their HIV status and ask about that of potential sex partners are very unlikely to choose a sex partner of opposite status [79]. The use of rapid tests as part of prevention strategies that promote the need for awareness of one's own and one's partner's infection status could reduce the sexual transmission of HIV considerably [80, 81].

The rationale for diagnostic testing has changed from clinical confirmation of suspected HIV disease to the potential for prevention and care afforded by knowing one's HIV status [39]. A wide range of HIV antibody tests are available. The challenge today is to identify the most suitable assays for a given set of circumstances without compromising the reliability of test results. It is essential to establish quality assurance programs so that both individuals and public health can reap the benefits of POC HIV testing with little risk of unreliable test results. It will be necessary to collect large amounts of data in settings of intended use to validate confirmatory algorithms comprised of POC rapid tests against the standards which have been proven. Given the frequent introduction of new rapid HIV tests, it is likely that such evaluations will need to be repeated frequently in field settings for the foreseeable future.

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