MAJOR ARTICLE

Multisite Laboratory Evaluation of a Dual Human Immunodeficiency Virus (HIV)/Syphilis Point-of-Care Rapid Test for Simultaneous Detection of HIV and Syphilis Infection

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Background. Recently, test developers have created rapid point-of-care tests that can simultaneously detect multiple infections within the same specimen using a single device. The SD BIOLINE Duo HIV/Syphilis rapid point-of-care test uses a solid-phase immunochromatographic assay to detect immunoglobulin (Ig)G, IgM, and IgA antibodies to human immunodeficiency virus (HIV)-specific antigens (HIV-1 gp41, sub O, HIV-2 gp36) and recombinant *Treponema pallidum* antigen (17 kDa) in human serum. This study was a multisite laboratory-based evaluation of the performance of SD BIOLINE HIV/Syphilis Duo test using previously characterized sera in 6 countries.

Methods. Laboratories in Ghana, Mexico, Laos, Togo, Kenya, and Myanmar participated in the evaluation during 2012–2013. Each site characterized sera using *T pallidum* particle agglutination assay or *T pallidum* hemagglutination assay and HIV enzyme immunoassay, Western blot, and/or HIV antibody rapid tests. Those gold standard test results were compared with SD BIOLINE Duo test results. We calculated the sensitivity and specificity of test performance and used the exact binomial method to calculate 95% confidence intervals (CIs).

Results. The sensitivity and specificity for the HIV antibody test component ($n = 2336$) were estimated at 99.91% (95% CI, 99.51% and 100%) and 99.67% (95% CI, 99.16% and 99.91%), respectively. For the *T pallidum* test component ($n = 2059$), the sensitivity and specificity were estimated at 99.67% (95% CI, 98.82% and 99.96%) and 99.72% (95% CI, 99.29% and 99.92%), respectively.

Conclusions. The sensitivity and specificity of the SD BIOLINE HIV/Syphilis Duo test were consistently high across sera specimens from 6 countries around the world. Dual rapid tests should be considered for improved HIV and syphilis screening coverage.

Keywords. HIV, Syphilis, Dual testing, test evaluation, rapid test.

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Syphilis is a curable disease, yet an estimated 1.4 million pregnant women are infected with syphilis each year, and 80% of these women had attend antenatal care services [1, 2]. Syphilis frequently has atypical presentations that may be difficult to differentiate from other sexually transmitted infections via history and physical examination, making effective diagnostics essential [3]. If syphilis remains untreated during pregnancy, it can lead to fetal loss or stillbirth or, in a live-born

infant, neonatal death, prematurity, low birth weight, or congenital syphilis [1, 4, 5]. In pregnant women who are infected with syphilis, adverse birth outcomes are common and have been shown to be 4.5 times higher in those with untreated syphilis than those without syphilis [5]. Congenital syphilis can be prevented by screening early in pregnancy, treating seropositive pregnant women, and preventing reinfection [4, 5].

In 2010, it was estimated that close to 1.5 million pregnant women were infected with human immunodeficiency virus (HIV), and only 35% of women (up from 8% in 2005) were estimated to have been tested for HIV [6]. HIV can be transmitted to the fetus during pregnancy and to the infant during labor or by breastfeeding. To reduce the rate of maternal-to-child transmission (MTCT) of HIV, HIV must be diagnosed and appropriate treatment and care must be provided [6]. In addition, syphilis infection during pregnancy greatly increases the risk of MTCT of HIV [3, 7].

Recently, the World Health Organization (WHO) has called for the dual elimination of MTCT HIV and syphilis, with new strategies and integrated monitoring and evaluation activities [8–10]. Screening for HIV and syphilis is highly recommended as part of a comprehensive dual elimination strategy [11–13]. The advent of integrated dual diagnostic tests for HIV and syphilis could provide a major breakthrough, facilitating integration of screening of syphilis into HIV prevention programs such as prevention of MTCT of HIV and targeted screening for high-risk populations. This integration would add little to the cost but would have a major effect on case finding of syphilis and the prevention of transmission [2, 14]. Implementing a simple and affordable dual test strategy for HIV and syphilis could improve screening uptake and accessibility of testing to accelerate time to treatment.

A rapid test is a simple point-of-care test that can be used in all healthcare settings to allow immediate treatment. It is easy to perform and does not require special storage or transport conditions. The result is easy to interpret and available after approximately 20 min. Point-of-care testing provides the opportunity for increased uptake of testing. Recently, test developers have created rapid tests that can detect multiple infections in the same specimen using a single device. The WHO outlined the ASSURED criteria for to evaluate point-of-care tests for use in resource-limited settings; affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end users [15, 16].

The SD BIOLINE HIV/Syphilis Duo test [17] is a qualitative detection method using a solid-phase immunochromatographic assay. This test meets the ASSURED criteria outlined by the WHO. This study was a multisite laboratory-based evaluation of the performance of the SD BIOLINE HIV/Syphilis Duo test using previously characterized serum samples from 6 countries.

METHODS

Study Sites and Population

A total of 6 study sites around the world participated in the evaluation study from 2012 to 2013. Study sites included laboratories in Ghana, Togo, Kenya, Mexico, Laos, and Myanmar. Specimens included stored sera that had previously been tested for syphilis and HIV infection according to local guidelines. The clinical settings for specimen collection included HIV and sexually transmitted disease testing sites in urban areas of the respective countries. The only processing that was done was serum separation, and trained laboratory personnel performed all testing. Reference testing was performed in accordance with national guidelines. Each laboratory had quality assurance protocols that comply with national and WHO standards.

Test for Evaluation

The SD BIOLINE Duo HIV/Syphilis rapid point-of-care test uses a solid-phase immunochromatographic assay to detect immunoglobulin (Ig)G, IgM, and IgA antibodies to HIV-specific antigens (HIV-1 gp41, sub O, HIV-2 gp36) and recombinant *Treponema pallidum* antigen (17 kDa) in human serum. The recombinant HIV-1/2 antigen, recombinant *Treponema palladium* antigen, colloid gold conjugate, the specimen sample and sample diluents move along the membrane chromatographically to the test region and form a visible line as the antigen-antibody-antigen gold particle complex forms [15].

Comparison Testing

Each country had previously characterized samples that were used in this evaluation. For gold standard testing, each country used a combination of *T pallidum* particle agglutination assay or *T pallidum* hemagglutination assay for detection of syphilis infection and enzyme immunoassay, Western blot, and rapid tests for the detection of HIV infection. The exact tests and algorithms used for characterization of serum samples are displayed in Tables 1 and 2.

Data Analysis

We calculated the sensitivity and specificity of test performance at each individual site using the exact binomial method to calculate 95% confidence intervals (CIs). Because we failed to find sufficient evidence against homogeneity of test performance between sites, we calculated a 95% CI using the exact binomial method on the combined data. We also considered a fixed effect and random effects logistic regression model to model the sensitivity and specificity in which the response variable was defined to be the dichotomous results of the screening test, a binary explanatory variable was defined by the "gold standard", and testing site indicators were included in the model to capture individual site effects [18, 19]. However, because there was near

Table 1. Country, Reference Tests, and Algorithms for HIV Characterization in Sera Specimens

Country	Reference Tests for HIV	Algorithms
Ghana	HIV I/II Genscreen (Bio-Rad, France)	Negativity was defined as negative on both tests.
	First response HIV 1-2-0 (PMC, India)	Positive specimens were positive on both tests.
Togo	Vironostika HIV1/2 Uniform II plus O (Biomérieux BV, Boxtel, The Netherlands)	If the EIA was negative then specimens were defined as HIV negative.
	Inno-lia (Innogenetics N.V. Belgium)	Specimens that were defined as positive were EIA-positive and Western blot-positive.
Myanmar	HIV Ag/Ab ELISA (Murex, UK)	Specimens testing negative on the ELISA test were defined as negative.
	HIV1/2 Stat-Pak (Chembio, New York, USA)	Positive results on the ELISA were confirmed using the rapid test.
Kenya	Determine RDT (Alere Medical Co. Ltd, Japan)	Specimens testing negative on both RDTs were defined as negative.
	Unigold RDT (Trinity Biotech plc, Bray, Ireland)	Those testing positive or discrepant on the 2 RDTs were confirmed using EIA in duplicate wells. Those positive on EIA were defined as positive.
	Vironostika HIV1/2 Uniform II plus O (Biomérieux BV, Boxtel, The Netherlands)	
Laos	Anilab HIV ELISA	The rapid test was used as the comparison to the evaluation test. When results were discordant, the ELISA was used as the confirmatory test.
	Standard Diagnostics HIV 1/2 3.0 rapid test	
Mexico	VITROS ECi/ECiQ Immunodiagnostic System Anti HIV 1 + 2 (Johnson & Johnson, UK)	Specimens that tested positive on the Vitros and Vironostika were defined as HIV positive. Those negative on both were defined as HIV negative. Discordant results were confirmed using the Western blot.
	Vironostika HIV1/2 Uniform II plus O (Biomérieux BV, Boxtel, The Netherlands)	
	New LAV Blot I (Bio-Rad, CA, USA)	

Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; RDT, rapid diagnostic test.

perfect test performance, the models failed to converge and yield sensible results. We were only able to fit the reduced simple logistic regression model on the combined data, and so we chose to report the exact binomial results only. Analyses were conducted using SAS, version 9.3 (Cary, NC). This analysis of deidentified laboratory data was determined to be exempt from human subject considerations.

Table 2. Reference Tests for *Treponema pallidum* Characterization in Sera Specimens

Country	Reference tests
Ghana	TPHA (Omega Diagnostics, Scotland)
Togo	TPHA (CYPRESS Diagnostics, Langdorp, Belgium)
Myanmar	Omega TPHA (Omega, UK)
Kenya	TPHA Kit (Randox Laboratories Ltd, UK)
Laos	Syphilis TPHA liquid (Human Diagnostics, Wiesbaden, Germany)
Mexico	IMMUTREP -USR (Omega Diagnostics, Scotland, UK)
	FTA- ABS Trepo Spot IF (BioMerieux, Marcy l'Etoile, France)

Abbreviations: EIA, enzyme immunoassay; TPHA, *T pallidum* hemagglutination assay.

RESULTS

Summarized results for each study site for HIV antibody test performance can be seen in Table 3. Results for each study site for *T pallidum* antibody test performance can be seen in Table 4. In total, 2336 HIV-characterized specimens and 2059 syphilis-characterized specimens were used to evaluate this HIV/Syphilis Duo kit across the 6 countries. The combined sensitivity and specificity for testing HIV status was 99.91% (95% CI, 99.51% and 100%) and 99.67% (95% CI, 99.16% and 99.91%), respectively. For the detection of antibodies to *T pallidum*, the combined sensitivity and specificity was 99.67% (95% CI, 98.82% and 99.96%) and 99.72% (95% CI, 99.29% and 99.92%), respectively.

DISCUSSION

We completed a study combining laboratory performance evaluations from 6 different laboratories across the world. The sensitivity and specificity of the dual HIV/syphilis test using serum were consistently high across 6 countries. Although there were some differences in the gold standard test algorithms, there was no apparent impact on test performance, which was greater than 99.7% sensitive and 97% specific across 6 countries for the detection of antibodies to HIV. In addition, test performance was above 98% sensitive and nearly 100% specific for detection of *T pallidum* antibody across 6 countries. Those findings of consistent high performance are similar to the high performance reported for single point-of-care tests for HIV and syphilis [20, 21].

Point-of-care tests can result in accelerated linkage to treatment and care by decreasing the time to result and can be used in settings with limited laboratory access [22]. Dual rapid tests with multiple analytes provide additional advantages by testing for multiple infections, and there is further efficiency

Table 3. Laboratory Performance for Detection of HIV Antibodies Using a Dual HIV/Syphilis Test in Previously Characterized Sera Samples in 6 Laboratory Sites

Country	Year	*n*	True Positives	False Positives	False Negatives	True Negatives	Sensitivity Estimate (exact 95% CI)	Specificity Estimate (exact 95% CI)
Ghana	2012	400	250	0	0	150	100% (98.54%, 100%)	100% (97.57%, 100%)
Togo	2013	310	203	0	0	107	100% (98.20%, 100%)	100% (96.61%, 100%)
Myanmar	2013	245	114	1	0	130	100% (96.82%, 100%)	99.24% (95.82%, 99.98%)
Kenya	2013	698	345	0	1	352	99.71% (98.40%, 99.99%)	100% (98.96%, 100%)
Mexico	2013	527	158	0	0	369	100% (97.69%, 100%)	100% (99.01%, 100%)
Laos	2013	156	53	3	0	100	100% (93.28%, 100%)	97.09% (91.72%, 99.40%)
Total	–	2336	1123	4	1	1208	99.91% (99.51%, 100%)	99.67% (99.16%, 99.91%)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

in using a single device and a single specimen. Multiplex diagnostic testing can increase uptake of screening for often ignored infections like syphilis [2, 13, 23]. With the large sum of donor funds available to support the prevention of MTCT of HIV infection, babies are increasingly avoiding HIV infection by HIV-infected mothers using effective programs, but infants are still at risk of dying of syphilis because of the lack of available syphilis screening [14]. Dual testing devices provide an opportunity for an infection like syphilis that has less community awareness and public health advocacy to be twinned into the same platform of diagnosis and therefore integrated into functional MTCT of HIV programs during routine antenatal visits and HIV testing. The expected cost for this rapid test is approximately $1.20 to $1.50 through WHO bulk procurement, which compares favorably to current WHO bulk procurement for single tests.

Other dual rapid tests for HIV and syphilis have been developed and evaluated and are showing promising results, such as the Multiplo Rapid TP/HIV Antibody Test (MedMira, Nova Scotia, Canada) and the DPP HIV-Syphilis Assay (Chembio, Medford, New York) [24, 25]. The high sensitivity and specificity shown in evaluations of these 2 tests are consistent with the high performance observed using the SD BIOLINE HIV/Syphilis Duo test evaluated in this study.

In a context where 1.5 million HIV-infected pregnant women deliver annually and 1.4 million pregnant women have syphilis each year, an integrated screening program is warranted to reduce the worldwide burden, transmission, and adverse effects of these diseases [1, 6, 26]. Rapid point-of-care dual testing comes at a time when the WHO and UNAIDS are scaling up programs for the dual elimination of MTCT of HIV and syphilis [8–10]. An integrated strategy of antenatal HIV and syphilis screening can reduce the adverse outcomes of syphilis during pregnancy and helps to reduce the MTCT of HIV and syphilis [22, 23, 27–29].

This study was subject to some limitations. First, this study was conducted using sera in laboratory settings. However, the test is optimally used as a point-of-care test in whole blood finger stick specimens. Additional evaluation should be considered in field settings to determine the performance outside of the laboratory. Second, the study was conducted independently at each country-site, and therefore the algorithm for characterizing serum specimens as HIV antibody or *T pallidum* antibody positive or negative varied. However, all samples underwent characterization with acceptable reference test algorithms. A major strength of this study was that it showed consistently high performance in all 6 settings around the world that have differing rates of infection and human antibody profiles.

Table 4. Laboratory Performance for Detection of *Treponema pallidum* Antibodies Using a Dual SD BIOLINE HIV/Syphilis Test in Previously Characterized Sera Samples in 6 Laboratory Sites

Country	Year	*n*	True Positives	False Positives	False Negatives	True Negatives	Sensitivity Estimate (exact 95% CI)	Specificity Estimate (exact 95% CI)
Ghana	2012	400	250	1	0	149	100% (98.54%, 100%)	99.33% (96.34%, 99.98%)
Togo	2013	241	88	1	0	152	100% (95.89%, 100%)	99.35% (96.41%, 99.98%)
Myanmar	2013	200	74	1	1	124	98.67% (92.79%, 99.97%)	99.20% (95.62%, 99.98%)
Kenya	2013	698	85	0	0	613	100% (95.75%, 100%)	100% (99.40%, 100%)
Mexico	2013	414	106	1	1	306	99.07% (94.90%, 99.98%)	99.67% (98.20%, 99.99%)
Laos	2013	106	6	0	0	100	100% (54.07%, 100%)	100% (96.38%, 100%)
Total	–	2059	609	4	2	1444	99.67% (98.82%, 99.96%)	99.72% (99.29%, 99.92%)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

Point-of-care tests are important for clinical settings that have none or limited laboratory access. Implementing a simple and affordable dual test for HIV and syphilis would improve screening uptake and accessibility of testing to accelerate time to treatment [22, 23, 27–29]. Such integration is a major step towards the comprehensive prevention of congenital infections.

CONCLUSION

The sensitivity and specificity of the SD BIOLINE HIV/Syphilis Duo test using sera was consistently high across specimens from 6 countries around the world. This dual test could be a timely breakthrough for the UNAIDS and WHO strategy for dual elimination of MTCT of HIV and syphilis and should be considered for improved HIV and syphilis screening coverage.

Notes

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