

Rapid point-of-care HIV testing in pregnant women: a systematic review and meta-analysis

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Summary

Rapid, point-of-care human immunodeficiency virus (HIV) testing has the potential to enhance strategies to prevent mother-to-child transmission (MTCT) of HIV infection. Rapid tests need minimal laboratory infrastructure and can be performed by health workers with minimal training. In our systematic review and meta-analysis, we aimed to summarize the overall diagnostic accuracy of rapid HIV tests in pregnancy, and outcomes such as acceptability, patient preference, feasibility and impact of rapid testing. We searched four major databases, identified and screened 1377 citations, and included 17 studies that met our eligibility criteria. Analyses of these studies suggested that the overall sensitivity and specificity of blood-based rapid tests was high compared with oral rapid tests. A two-step testing strategy, particularly parallel testing, was found to be superior to single-test strategy in labour and delivery settings. Acceptability of rapid tests and patient preference was variable across studies. Overall, rapid HIV testing was highly accurate compared with conventional tests and offer a clear advantage of enabling the implementation of timely interventions to reduce MTCT of HIV. To improve diagnostic accuracy and to reduce false-positive results, it may be necessary to use two rapid tests during labour and delivery.

keywords HIV, rapid test, pregnancy, perinatal screening, mother-to-child transmission

Introduction

In recent years, the human immunodeficiency virus (HIV) pandemic has significantly affected young adults, particularly women of reproductive age (15–44 years) (UNAIDS 2004; WHO 2004a,b). Increases in HIV seroprevalence in women primarily caused by heterosexual transmission, and childbearing in developing countries, has led to an increase in risk of vertical transmission of HIV to infants in the absence of antiretroviral (ARV) therapy (UNAIDS 2004; WHO 2004a,b). In 2004, a majority (95%) of new HIV infections were detected in low and middle income countries and, of these, 50% of the infections were detected in women. About 640 000 new HIV infections were detected in children in the same year (UNAIDS 2004; WHO 2004a,b). The proportion of children who acquired HIV in perinatal settings was in the range of 90–95% (UNAIDS 2004; WHO 2004a,b). In this context, prevention of mother-to-child transmission (MTCT) is critically important.

In developing countries, a sizeable proportion of pregnant women seek medical care only during the time of labour and delivery, with no previous antenatal care

whatsoever ('un-booked pregnancies') (Matambo *et al.* 1999). In such settings, home deliveries are also common. Lack of any antenatal care implies that these women have no opportunities for HIV counselling and testing prior to delivery (WHO 2004a,b). Testing during labour, therefore, provides the last window of opportunity for interventions to decrease HIV transmission to the newborn (Bulterys *et al.* 2004). Effective interventions are now available to reduce the risk of MTCT, even if implemented during intrapartum or immediate post-partum period (i.e. short course ARV therapy to the woman and infant, and in some settings, Caesarean section delivery and bottle feeding).

To accomplish the objective of reducing MTCT, administration of a package of interventions, including ARV therapy, elective Caesarean section, modification of infant feeding practices have been recommended by the WHO (2004a,b). Primary prevention is the first step, and knowledge of HIV serostatus is an important starting point to achieve this objective (WHO 2002). Therefore, an efficient, accessible, voluntary testing and counselling programme is a prerequisite to the institution of an effective MTCT programme (WHO 2004a,b)

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The current standard and conventional method for the diagnosis of HIV is initial screening with an enzyme immunoassay (EIA) test followed by a confirmatory Western blot. In contrast to conventional HIV testing methods, newer, rapid tests have many advantages. Test results are obtained faster (e.g. <1 h), in contrast to conventional testing that may take up to a week. This delay in obtaining test results can lead to missed opportunities to prevent MTCT, and also increase chances of loss to follow-up (Downing *et al.* 1998; Branson 2003). Rapid tests need minimal laboratory infrastructure and can be performed by health workers with minimal training, with adequate quality controls (Downing *et al.* 1998; Branson 2003; Granade *et al.* 2004). Rapid point-of-care HIV testing has great potential to enhance prevention of MTCT.

There is some evidence that pregnancy may alter the accuracy of HIV testing, therefore an analysis specifically focused on studies in pregnant women is warranted. False-positive test results occur in pregnancy because of multiparity, multiple previous blood transfusions, and autoimmune disorders. These factors lead to a generalized immune stimulation, inducing production of antibodies that cross react with HIV antigens (Doran & Parra 2000; Zacharias *et al.* 2004). Testing during the early stages of HIV infection is a problem. In early stages of HIV infection, indeterminate Western blots are sometimes seen, because of delay in the appearance of antibodies. In late stages of HIV infection, patients are symptomatic and not difficult to diagnose clinically. Indeterminate Western blot in late stages may be due to impairment in antibody production due to generalized immunodeficiency (Doran & Parra 2000).

In our systematic review and meta-analysis, we aimed to: (i) summarize the overall diagnostic accuracy of rapid HIV tests in pregnancy; (ii) evaluate outcomes such as uptake of tests (acceptability), patient preference, feasibility and impact of testing; and (iii) identify practical challenges related to the implementation of voluntary testing and counselling in pregnant women.

Methods

Search strategy and identification of studies

To identify potentially eligible studies, we searched four electronic databases covering the period from January 1991 to July 2005, for journal articles as well as conference abstracts. The databases searched were PubMed (1990–2005), Web of Science (1990–2005), EMBASE (1990–2005), and BIOSIS (1990–2005). We searched bibliographies and references of relevant primary studies and review articles. We also contacted experts in the field

for additional studies. The search terms used for database searching included both MeSH* and free text terms. The search string used included the following terms: 'HIV seropositivity*', 'acquired immunodeficiency syndrome*', 'HIV*', 'HIV antigens*', 'HIV antibodies*', 'reagent kits, diagnostic*', 'rapid test', 'point of care tests', 'pregnant women', 'antenatal care*', 'delivery', 'labor', and 'mother to child transmission*'.

Study selection

Two reviewers independently screened the citations. Citations found relevant in the first screen were evaluated by review of full text reports. Disagreements were resolved by consensus. We included studies evaluating rapid tests in pregnant women in antenatal clinics, and delivery room settings. We included survey reports and abstracts providing complete information. We excluded letters, review articles, commentaries, and editorials. Only English language publications were included.

Data abstraction

The final data abstraction was carried out by one reviewer. A pre-piloted data abstraction form was used to abstract data. The data extracted included study setting, type of laboratory, type of test used, samples tested, participant characteristics, objectives of testing, reference standard, diagnostic accuracy (sensitivity and specificity), agreement between oral and blood-based rapid tests, and other outcomes (HIV prevalence, uptake, patient preference, challenges of counselling).

Quality assessment of included studies

Diagnostic studies are typically cross-sectional studies, or case-control studies. Sampling may be probabilistic (computer-generated sequence of random numbers) or non-probabilistic (convenience sampling). There is potential for selection bias when selection methods are non-probabilistic. If hospitalized patients with severe illness are recruited into the study, sensitivity estimates may be inflated and selection bias is more pronounced. Surveys use random or probabilistic sampling method and recruit a spectrum of study participants at one point in time. Participants are fairly representative of the population sampled. Case-control studies, where cases and controls are sampled from two extreme ends of clinical spectrum, tend to overestimate diagnostic accuracy (Knottnerus 2002).

To evaluate the quality of included studies, we used the validated QUADAS (Quality Assessment of Diagnostic Accuracy of Studies) instrument for diagnostic studies

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(Whiting *et al.* 2003). This checklist includes study design, selection of participants, reporting of exclusion and inclusion criteria, blinded interpretation of index and reference test, and verification bias (complete, partial, differential verification of index test results with the reference standard) (please refer to Table 1).

Statistical analysis and data synthesis

We used standard methods recommended for meta-analyses of diagnostic test evaluations. Data were analysed with META-DISC (Ver. 1.2) software. Our analyses focused on the following measures of diagnostic accuracy: sensitivity (true positive rate, TPR), and specificity [$1 - \text{false positive rate (FPR)}$].

Each study in the meta-analysis contributed a pair of numbers: TPR and FPR. As these measures are correlated and vary with the thresholds (cut points), it is customary to analyse TPR and FPR proportions as pairs, and to also explore the effect of threshold on study results. We summarized the joint distribution of sensitivity and specificity using the Summary Receiver Operating Characteristic (SROC) curve. Unlike a traditional ROC plot that explores the effect of varying thresholds on sensitivity and specificity in a single study, each data point in the SROC space represents a separate study.

The SROC curve is obtained by fitting a regression curve to pairs of TPR and FPR (Littenberg & Moses 1993). The area under the SROC curve presents an overall summary of

test performance, and displays the trade-off between sensitivity and specificity. A symmetric, shoulder-like SROC curve suggests that variability in thresholds employed could, in part, explain variability in study results (Littenberg & Moses 1993). The area under the SROC curve is a global measure of overall test accuracy. An area under the curve of 100% indicates a perfect discriminatory ability. In our paper, the area under the curve is close to 100%.

In the presence of significant heterogeneity, pooled, summary estimates from meta-analyses are not meaningful. Heterogeneity was assessed using the chi-squared test for heterogeneity. We also investigated heterogeneity using subgroup analyses, based on specimen type. Meta-regression was not attempted due to the small number of studies identified. Heterogeneity could be explained by different samples used for testing, different index tests, different kits with varying sensitivities and specificities, different and inadequate reference standards, diversely recruited study populations from different countries, different study designs, different study settings, and different testing algorithms (serial, parallel, single tests).

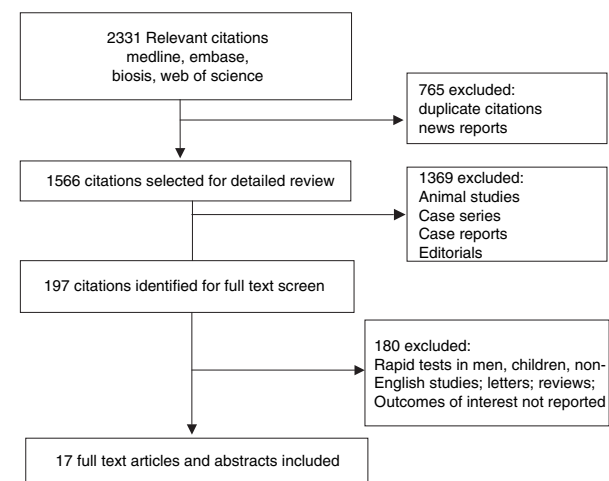
Results

Figure 1 shows the study selection process. After the initial screening of 1566 citations, 197 citations were selected for full text review. Of these, 37 studies were evaluated for eligibility, and 17 studies were included in the final analyses. Only studies conducted in pregnant women were included.

Although 17 studies qualified for the review, they reported different outcomes. Classification by outcomes is

Table 1 Quality of studies included in the review

Study characteristics	Frequency (%)
Study design	
Cross-sectional	13
Case-control	0
Surveys	4
Verification of rapid tests with reference standard	
Complete	0
Partial	12
Unclear/not reported	5
Direction of the study	
Prospective	15
Retrospective	2
Blinded interpretation of test results	
Reported	1
Not reported	16
Inclusion and exclusion criteria	
Reported	4
Not reported	13
Reference standard	
Single test	3
Composite	14

**Figure 1** Flow diagram of study selection.

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presented in the tables. Only seven studies reported diagnostic accuracy outcomes and were included in the meta-analyses. Of these, some studies (Webber *et al.* 2001; Granade *et al.* 2005; Bhore *et al.* 2003; Rouet *et al.* 2004) used multiple rapid HIV test kits, due to which 14 comparisons are tabulated in the test accuracy tables, forest plots and ROC curves. The remaining seven studies did not report diagnostic accuracy estimates, but reported other outcomes like acceptability, seropositivity, and preference. Five studies reported acceptability, nine reported HIV seropositivity and one reported on patient preference (please refer to Figures 2 and 3).

Description of included studies

Table 2 presents the description of the 17 included studies, along with the diagnostic accuracy estimates. Table 3 presents data on methodological quality of these studies. A majority (77%) of the included studies used the cross-sectional design, and a small number were population-based surveys. Study sample sizes varied from 106 to 4849. Patient demographics were poorly reported in many studies. The age of participants varied from 18–44 years.

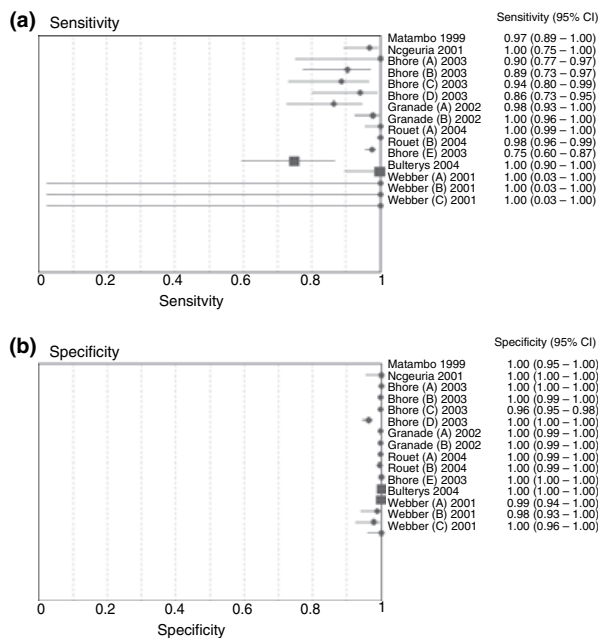


Figure 2 Forest plot of sensitivity and specificity for blood-based and oral rapid HIV tests. The point estimates of sensitivity and specificity for each study are shown as solid circles and squares with error bars (95% confidence intervals). Solid squares represent oral rapid tests and solid circles represent blood-based rapid tests.

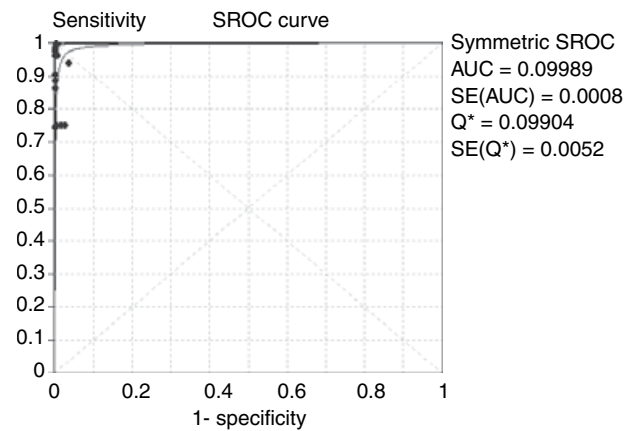


Figure 3 Summary receiver operating characteristic (SROC) plot for rapid HIV tests. Each solid circle represents a study in the meta-analysis. The SROC curve is a regression line that summarizes the overall diagnostic accuracy of tests. Q* index is defined as the point on the SROC curve, where the sensitivity and specificity are equal, which is the point closest to the top left corner of ROC space. AUC is area under the SROC curve.

Studies were conducted worldwide, four in the USA (Weber *et al.* 1998; Rajegowda *et al.* 2000; Bulterys *et al.* 2004; Forsyth *et al.* 2004), six in Africa (Matambo *et al.* 1999; Bakari *et al.* 2000; Granade *et al.* 2005; Malonza *et al.* 2003; Rouet *et al.* 2004; Rakgoasi 2005), three in Latin America (Nogueira *et al.* 2001; Hillyer *et al.* 2002; Perez-Then *et al.* 2003), two in South-east Asia (Bhore *et al.* 2003; Shankar *et al.* 2003) and one in Jamaica (Johnson *et al.* 2004). Studies were conducted in antenatal clinics and delivery rooms located in the hospitals or referral centres (Hillyer *et al.* 2002; Bhore *et al.* 2003; Bulterys *et al.* 2004; Forsyth *et al.* 2004).

The objectives of testing (screening, surveillance, or confirmation of diagnosis) were clearly reported across studies. Patient sampling method was not clearly reported in studies. In a majority (76%) of studies, a non-random (convenience) sampling methodology was employed. In terms of recruitment, the inclusion and exclusion criteria were clearly reported in only four studies. HIV positivity varied depending on populations tested. Positivity was as high as 45% in one study in antenatal clinic in Nairobi (ref), to 1.5% in another study conducted in a community hospital (ref). In many studies, women with varying levels of high risk behaviour were tested.

Blood-based rapid tests were used in 12 studies (71%). Oral rapid tests were used in five studies (29%) (Bhore *et al.* 2003; Bulterys *et al.* 2004). Rapid tests evaluated included OraQuick® (OraSure Technologies, USA), Capillus® (Trinity Biotech, Ireland), SUDS® HIV-1 (Murex

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Author	Sample size	Site	Rapid HIV test and specimen used	Reference standard	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %
Matambo <i>et al.</i> 1999, South Africa	160	ANC	Capillus [®] Blood	EIA	97 (88.5-99.5)	100 (95.5-100)	100	97.5
Nogueira <i>et al.</i> 2001, Brazil	841	ANC	Determine [®] + Double Check [®] Blood	2 EIA + WB	100 (75.3-100)	100 (99.6-100)	100	100
Bhore <i>et al.</i> 2003, India (A)	1253	ANC/DR	OraQuick [®] finger stick	2 EIA	90.3 (72.7-94.8)	99.9 (99.5-100)	95.5	97.4
Bhore <i>et al.</i> 2003, India (B)	1013	ANC/DR	Determine [®] Blood	2 EIA	88.6 (73.3-96.8)	99.9 (99.4-100)	99.6	96.4
Bhore <i>et al.</i> 2003, India (C)	749	ANC/DR	Cadilla [®] Blood	2 EIA	94.1 (80.3-99.3)	96.4 (94.7-97.6)	99.7	55.2
Bhore <i>et al.</i> 2003, India (D)	1250	ANC/DR	OraQuick [®] plasma	2 EIA	86.4 (72.2-94.8)	99.9 (99.5-100)	99.5	96.4
Bhore <i>et al.</i> 2003, India (E)	1258	ANC/DR	OraQuick [®] HIV1/2 Oral	2 EIA	75 (59.7-86.8)	100 (99.7-100)	100	99.1
Bulterys <i>et al.</i> 2004, USA	4849	ANC/DR	OraQuick [®] Oral	EIA + WB	100 (90-100)	99.9 (99.78-99.98)	89.5	100
Granade <i>et al.</i> 2005 (A), Cameroon	859	ANC/DR	Serial testing Determine [®] , HemaStrip [®] , and Capillus [®] Blood	EIA + WB	97.6 (92.5-99.7)	99.7 (99.0-100)	97.8	99.7
Granade <i>et al.</i> 2005 (B), Cameroon	859	ANC/DR	Parallel testing Determine, HemaStrip [®] , and Capillus [®] Blood	EIA + WB	100 (95.7-100)	99.7 (99.0-100)	97.7	100
Rouet <i>et al.</i> 2004 (A), Cote d'Ivoire	1039	ANC	Determine [®] Blood	EIA + WB	100 (99.1-100)	98.4 (99.4-100)	100	98.5
Rouet <i>et al.</i> 2004 (B), Cote d'Ivoire	1039	ANC	Genie II [®] Blood	EIA + WB	99.5 (99.1-100)	100 (99.7-100)	99.5	100
Webber <i>et al.</i> 2001, USA (A)	106	Hospital	ELISA	EIA	100 (3.0-100)	99 (94.0-100)	33.3	100
Webber <i>et al.</i> 2001, USA (B)	106	Hospital	SUDS [®] Blood	EIA	100 (2.5-100)	98 (94.2-100)	33.3	100
Webber <i>et al.</i> 2001, USA (C)	106	Hospital	Multispot [®] Blood	EIA	100 (2.5-100)	100 (96.1-100)	100	100

ANC, antenatal clinic; EIA, enzyme immunoassay; WB, Western Blot DR delivery room.

Table 3 Studies investigating uptake/acceptability of rapid HIV testing ($n = 5$)

Author	Country	Sample size	Participants	Rapid HIV test	Reference standard	Uptake (acceptability)
Rajegowda <i>et al.</i> 2000	USA	462	Hospital	SUDS [®] Blood	WB	85.7%
Webber <i>et al.</i> 2001	USA	125	Hospital	SUDS [®] , Multispot [®] Blood	EIA	85%
Malonza <i>et al.</i> 2003	Nairobi	1249	ANC	Capillus [®] + Determine [®] Blood	EIA	97%
Shankar <i>et al.</i> 2003	India	417	ANC and DR	NR	NR	83%
Rakgoasi <i>et al.</i> 2005	Botswana	4494	BAIS Survey participants	NR	NR	79%

ANC, antenatal clinic; EIA, enzyme immunoassay; WB, Western blot; NR, not reported.

Corp., USA), HemaStrip[®] (ChemBio, USA), Determine[®] (Abbott Diagnostics, USA), Genie II[®] (BioRad Laboratories, USA), and DoubleCheck[®] (Orgenics, Israel).

Reference standard varied across studies. In six (35%) studies, double enzyme-linked immunosorbent assay (ELISA) was used (Matambo *et al.* 1999; Hillyer *et al.* 2002; Bhore *et al.* 2003; Malonza *et al.* 2003), and two repeatedly reactive ELISA followed by Western blot were used in 24% of studies. A single Western blot was the reference standard in one study (Rakgoasi 2005).

Diagnostic studies, in general were weak in methodological reporting. Biases detected were verification, spectrum, incorporation, selection, and referral bias. Partial verification of index test was reported in all studies. Verification bias is present if a study selects participants for disease verification by gold standard on the basis of positive results of preliminary tests. Verification of test result refers to selection of study participants for disease verification by gold standard, based on preliminary rapid test results. Partial verification, also called work up bias results if only a subsample of participants verifies test results using a reference standard of diagnosis. In other words, verification of only positive test results by reference standard and incomplete evaluation of negative test results, would lead to partial verification (Knottnerus 2002).

A composite reference standard was used in a majority (80%) of studies. Composite refers to use of patient profile and results of index tests as surrogate for gold standard reference test. Clinical staging (signs and symptoms of HIV, presence of opportunistic infections and past HIV test result) were also used to diagnose HIV disease.

Spectrum bias was present in three studies. Spectrum bias is reported to be present when a diagnostic test has varying specificities and sensitivities in patients with varying clinical manifestations of disease. Selection bias was also reported to present when patient selection was

non-random; and convenience sampling was employed. This was present in six studies.

Diagnostic accuracy

Overall sensitivity of all rapid tests ranged from 75% to 100%. Overall, specificity of all rapid tests varied from 96.4% to 100%. In subgroups based on specimen type, blood-based tests, had high sensitivity (86.4–100%) and high specificity (99.5–100%). Oral fluid tests has moderate sensitivity from 75% to 100%, and high specificity from 99.9% to 100%. There were only two studies that investigated the use of oral fluid tests, and in one reference standard was inaccurate, therefore, sensitivity was underestimated. However, in the other study with a large sample size “Mother Infant Rapid Intervention at Delivery” (MIRIAD), high sensitivity 100% (90–100%) and specificity 99.9% (99.8–99.9%) estimates were reported.

Specificities of rapid tests were high, and comparable in both blood-based and oral tests. Sensitivity estimates were generally lower than high specificity estimates. In one study, the authors specifically discussed the limitations of the use of reference standards such as ELISA of lower specificity which underestimated sensitivity (Bhore *et al.* 2003).

A sequential rapid testing algorithm refers to the use of multiple rapid tests of different antigenic specificities in serial or parallel design. In a serial testing design, a sample is first subjected to a single rapid test, if it turns out non-reactive, it is declared seronegative. If it turns out reactive, the sample is subjected to a second rapid test and concordant reactive result is reported as seropositive. Resolution of discordance is done by use of a third test, which if reactive, the serologic status is reported by the best of three agreement. In the parallel testing design, a sample is simultaneously subjected to two rapid tests (parallel). Concordant sero-reactivity or non-reactivity is reported as

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seropositive, or seronegative. Discordance is resolved by reactivity of a third test, and serologic status is reported by best of three agreement. (Singer *et al.* 2005)

In four studies, a significant improvement in sensitivity and specificity estimates was reported with the use of a sequential rapid testing algorithm (Webber *et al.* 2001; Granade *et al.* 2005; Bhore *et al.* 2003; Rouet *et al.* 2004). A sequential rapid testing algorithm also decreases the possibility of missing cases. This had implications in emergent settings like delivery room and labour. Positive predictive values varied from 33.3% to 100%. Negative predictive values varied from 55.2% to 100%.

Uptake (acceptability) of rapid tests

Uptake of rapid tests by patients was reported as acceptability of rapid tests and its estimate varied from 83% to 97% (Malonza *et al.* 2003; Shankar *et al.* 2003; Bulterys *et al.* 2004). Two studies investigated factors associated with acceptability of testing. Overall, an increased uptake of rapid testing by pregnant women was associated with age >21 years, higher educational status, gestational age <32 weeks, and lack of adequate prenatal care during pregnancy (Bhore *et al.* 2003; Bulterys *et al.* 2004). In the largest study reported so far, the factors associated with acceptance of HIV testing after adjusting for study sites, were Hispanic ethnicity, gestational age <32 weeks, and absence of prenatal care (Bulterys *et al.* 2004). Rakgoasi *et al.* (2005) reported on predictors for testing and HIV counselling. In their study, younger and more educated people and town residents were more likely to accept HIV counselling than the rural uneducated people.

Patient preference for rapid tests

Two studies reported on this outcome. In one study, women preferred oral rapid tests (33%) over blood-based rapid tests (Melvin *et al.* 2004), in this study, details of how preference was assessed were unclear. In another

study, patients preferred finger stick (blood based tests) over salivary tests. Low preference of women for salivary tests were because of difficulty in obtaining adequate sputum for testing. There was no influence of age, parity and education over choice of rapid tests. (Shankar *et al.* 2003). Overall, there was no clear consensus, on patient preference of one method of rapid testing (blood based) over another (oral fluid based) (Table 4).

Impact of testing and counselling on women

Few studies reported on the impact of testing and counselling and linkage to care and prevention. Details of linkages to care and prevention were not reported. Three studies that did not evaluate accuracy of rapid testing among pregnant women, instead aimed to identify barriers to obtaining consent for HIV testing among women in labour were also reviewed. In these studies, counselling was identified as a challenging endeavour during labour and delivery. Investigators suggested an abbreviated, pre-test mini counselling session, during labour followed by an extensive post-partum counselling (Minkoff & O'Sullivan 1998; Jamieson *et al.* 2003; Shankar *et al.* 2003).

Pretest and post-test counselling sessions were not reported in greater detail in many studies, as test results were limited to diagnostic accuracy. It is to be emphasized that testing in pregnancy has the potential to affect emotional health of mother, baby and the family. Issues related to confidentiality of test results, test delivery and follow-up and care, were not clearly discussed or reported.

Jamieson and colleagues conducted a pre-MIRIAD evaluation of consent process. They did mock consenting among women who already knew their HIV status just to see if labouring women were 'consentable' *per se*. In this study, 70% women could state the purpose and benefit of the study. Understanding of purpose, benefit and risks of the study was also assessed. Refinement of the approach by the use of visual aids was recommended to improve effective delivery (Jamieson *et al.* 2003).

Table 4 Studies investigating patient preference for rapid testing (*n* = 1)

Author	Country	Sample size	Participants	Rapid HIV test	Reference standard	Patient Preference
Shankar <i>et al.</i> 2003	India	417	ANC Delivery room	OraQuick® Determine® Cadilla®	EIA	Blood based 43% ANC 48% DR Saliva brush 36% ANC 20% DR

ANC, antenatal clinic; DR, delivery room; NR, not reported.

Table 5 Cross-sectional studies reporting HIV positivity ($N = 9$)

Author	Country	<i>n</i>	Patient	Specimen	Index test	Reference test	HIV+
Matambo <i>et al.</i> 1999	South Africa	160	ANC	Blood	Capillus [®] Blood	EIA	45.2%
Bakari <i>et al.</i> 2000	Zambia	82	ANC	Blood	Dipstick [®] Blood	Capillus [®]	24.5%
Nogueira <i>et al.</i> 2001	Brazil	841	ANC	Blood	Determine [®] DoubleCheck [®] Blood	2EIA+ WB	1.5%
Hillyer <i>et al.</i> 2002	Puerto Rico	971	Hospital	NR	NR	EIA	2.26%
Malonza <i>et al.</i> 2003	Nairobi	1249	ANC	Blood	Capillus [®] + Determine [®] Blood	EIA	12.9%
Bhore <i>et al.</i> 2003	India	1258	ANC/DR	Oral/blood	OraQuick [®] Oral Determine [®] Cadilla [®] Blood	2EIA	3.49%
Bulterys <i>et al.</i> 2004	USA	4849	DR	Oral	OraQuick [®] Oral	EIA + WB	0.7%
Johnson <i>et al.</i> 2004	Jamaica	19 414	Outpatient/ inpatient	Blood	Determine [®]	ELISA	2.1%
Perez-Then <i>et al.</i> 2003	Dominican Republic	23 067	ANC/DR	NR	NR	NR	2.5%
Forsyth <i>et al.</i> 2004	USA	156	Hospital A Hospital B	Blood	SUDS [®] blood	SUDS + EIA	NR
Melvin <i>et al.</i> 2004	Peru	3543	DR	Oral/blood	OraQuick [®] Oral Determine [®] Blood	NR	NR

ANC, antenatal clinic; DR, delivery room; NR, not reported.

Shankar *et al.* (2003) reported a similar method to assess the uptake of testing which was high (83%) in a rural patient population in resource-limited setting. They also assessed the role of husband's support in HIV testing. Husbands (97%) supported their wives' decision to test, and high level (69%) of independent decision making by wives on testing. Testing pregnant women for protection of child was reported to be socially acceptable (Table 5).

Barriers to testing

In one study by Malonza *et al.* (2003), obstacles to attendance at the antenatal clinic were assessed; this could act as barriers to testing. These were travel costs to testing site, preference for home delivery. Besides, fear of disclosure of HIV-1 test results and partner notification, were also important in preventing women to get tested during antenatal period.

HIV-1 and HIV-2

There was no mention of test performance on the basis of HIV1/HIV2.

Discussion

Overall, diagnostic accuracy of rapid tests was high. Sensitivity was reported lower than specificity in a few studies. In largest study (MIRIAD) using OraQuick, sensitivity and specificity of oral tests was reportedly high (100% and 99.9%).

Lower estimates of sensitivity in small studies, could be explained by insufficient samples, different test kits, inaccurate evaluation, inappropriate reference standard, varying test methods, and variable patient spectrum. The US Centers for Disease Control and Prevention (CDC) recommended reference standard for rapid testing is EIA and Western Blot, which is most commonly used. Alternatively, other confirmatory methods such as immunofluorescence assays and radioimmunoprecipitation assays are also used (CDC 2004). In some studies, only one EIA, two EIA, or one Western Blot has been used as reference standard. These are considered 'inadequate reference standards.'

Lower estimates of sensitivity increases false negatives. Use of appropriate reference standard affects diagnostic accuracy estimates. To decrease chances of missing cases, it

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was suggested to incorporate two-step sequential testing algorithm during labour and delivery (Nogueira *et al.* 2001; Webber *et al.* 2001; Granade *et al.* 2005; Bhole *et al.* 2003). To be able to improve accuracy estimates, using sequential testing algorithm, test diagnostic accuracy estimates, test specimens, and order of its use were important.

In all reported studies, specificity was reportedly high. Of all the studies reviewed, only four studies used Western blot for confirmation. Resolution of indeterminate test results was not clearly reported. It is possible, that in studies where ELISA was used as reference standard, specificity would have been overestimated.

In studies where two-step testing procedure were employed, sensitivity estimates improved significantly (Nogueira *et al.* 2001; Webber *et al.* 2001; Granade *et al.* 2005; Bhole *et al.* 2003). Only one study evaluated two-step testing procedures, and reported parallel testing being superior to serial testing (Granade *et al.* 2005). In contrast to sensitivity, specificity was consistently high across studies.

Different reference standards were used across populations. This affected the interpretation of diagnostic accuracy. In all the studies, Western blot was not always used to confirm index test results. Cost of the test could be a potential determinant in deciding Western blot results.

Acceptability for rapid tests was high across populations. Acceptability was not clearly defined, and details of how it was assessed in the questionnaire were not reported. Based on logistic regression model results, significant predictors were reported. Acceptability referred to patient's uptake of testing in labour, delivery and antenatal care settings. Although, it was not clear whether uptake of testing implied patient's satisfaction with all or any aspect of testing (pretest counselling, testing procedure, test result, post-test counselling), or whether patients were interested in getting tested for determination of HIV status and benefit of interventions that followed.

Counselling was identified as challenging exercise (confidentiality of test result, privacy, and time available to address questions and pain during labour). A two-phase counselling session was suggested by investigators (Jamieson *et al.* 2003; Shankar *et al.* 2003). A mini counselling session during labour with the use of effective visual aids explaining key interventions during labour, followed by an extended second post-partum counselling session, was recommended to allow time for questions regarding risk reduction and interventions during the post-natal period.

CDC now recommends 'opt-out' HIV testing for pregnant women whereby women are informed that HIV testing will be performed unless they specifically opt-out or

decline the testing, there is limited counselling with this approach.

Implications for practice

A two-step testing strategy, particularly parallel testing, is superior to single test strategy in a labour and delivery setting and should be used in clinical settings. This improves diagnostic accuracy estimates, by decreasing false positives and false negatives. It also has great bearing on the emotional health of the mother during delivery, and post-partum period. It affects decision-making abilities of the providers and affects treatment choices and should not be ignored. Effective counselling techniques need to be more fully evaluated. A greater emphasis on two-phase counselling and effective delivery and comprehension of intervention and sustainability of benefit needs to be explained. An effective prevention of MTCT programme can work well if women are identified early in pregnancy. Ideally, this would happen, early in pregnancy, but social, cultural, barriers in many settings precludes such early diagnosis.

Implications for research

Future studies comparing parallel and serial testing strategies, and those exploring use of oral fluid-based tests are needed. Studies evaluating effect of using different reference standards on diagnostic accuracy estimates are also needed. Research on impact of testing pregnant women, with documentation of loss to follow-up, and linkages with care and prevention programmes are needed. These data will guide policy on improving voluntary counselling and testing using rapid tests.

Strengths and limitations of the review

Our review had several strengths. We performed a comprehensive search of several databases and sources to identify studies. We contacted authors for original study articles. We evaluated the quality of included studies using established quality criteria. Screening for study eligibility was performed by two reviewers. We also explored all outcomes including a meta-analysis for diagnostic accuracy. Our review had some limitations. A majority of studies were conducted using blood-based rapid tests. We therefore had insufficient data to estimate the accuracy of oral fluid-based rapid tests. We were unable to perform a meta-regression to explore heterogeneity, as we had few studies and data points. Statistical comparison between subgroups was also not possible because of lack of data. We tried to minimize publication bias by including both

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published studies and abstracts. We included only English language studies, and this may have led to reporting bias.

Conclusion

In settings, where pregnant women present for testing for the first time during delivery, rapid test use is ideal diagnostic test. Our review suggests that rapid test have high diagnostic accuracy, and improved estimates with a two-step testing strategy. Uptake and preference for these tests are also reportedly high.

Use of an appropriate reference standard is important as it leads to underestimate or overestimate of diagnostic accuracy. All the studies with appropriate reference (two rapid tests confirmed with two ELISA) or (two rapid tests confirmed with two ELISA and Western blot) reported superior estimates of sensitivity and specificity. To improve estimates of diagnostic accuracy and to reduce false positives, it is recommended to use two rapid tests during labour and delivery. Diagnostic accuracy estimates were comparable with conventional ELISA and Western blot. Parallel testing strategy was slightly better than serial rapid testing strategy. Both blood-based and oral rapid tests were highly accurate. They can be routinely recommended in settings; however, it is difficult to validate confirmatory testing algorithms using different combinations of rapid tests with varying sensitivity and specificity (Branson 2003). Rapid testing was overall feasible, highly accurate compared with conventional tests and offers the clear advantage of enabling the implementation of timely interventions to reduce MTCT of HIV. The implementation of rapid HIV testing among pregnant women could have substantial impact on the HIV epidemic worldwide.

Acknowledgements

This work was supported in part by the National Institutes of Health (NIH), Fogarty AIDS International Training Program (1-D43-TW00003-17). The NIH had no role in the design, preparation, review, or approval of this manuscript. We thank Madhukar Pai, MD, for helpful comments on an earlier draft of this manuscript, and Rajnish Joshi, for assistance with database searches and screening.

References

- Bakari JP, Mckenna S, Myrick A, Mwinga K, Bhat GJ & Allen S (2000) Rapid voluntary testing and counseling for HIV: acceptability and feasibility in Zambian antenatal care clinics. *Annals of the New York Academy of Sciences* **918**, 64–76.
- Bhore AV, Sastry J, Patke D *et al.* (2003) Sensitivity and specificity of rapid HIV testing of pregnant women in India. *International Journal of STD and AIDS* **14**, 37–41.
- Branson BM (2003) Point-of-care rapid tests for HIV antibodies. *Laboratoriums Medizin* **27**, 288–295.
- Bulterys M, Jamieson DJ, O'Sullivan MJ *et al.* (2004) Rapid HIV-1 testing during labor – a multicenter study. *JAMA* **292**, 219–223.
- CDC (2004) *Rapid HIV-1 antibody testing during labor and delivery for women of unknown HIV status: a practical guide and model protocol*. Centers for Disease Control and Prevention. http://www.cdc.gov/hiv/rapid_testing/rt-labor&delivery.htm#intro3.
- Doran TI & Parra E (2000) False-positive and indeterminate human immunodeficiency virus test results in pregnant women. *Archives of Family Medicine* **9**, 924–929.
- Downing RG, Otten RA, Marum E *et al.* (1998) 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.
- Forsyth BWC, Barringer SR, Walls TA *et al.* (2004) Rapid HIV testing of women in labor: too long a delay. *JAIDS: Journal of Acquired Immune Deficiency Syndromes* **35**, 151–154.
- Granade TC, Parekh BS, Phillips SK & Mcdougal JS (2004) Performance of the OraQuick and Hema-Strip rapid HIV antibody detection assays by non-laboratorians. *Journal of Clinical Virology* **30**, 229–232.
- Granade TC, Parekh BS, Tih PM, Welty T, Welty E, Bulterys M, Ndikintum G, Nkuoh G & Tancho S (2005) Evaluation of rapid prenatal human immunodeficiency virus testing in rural Cameroon. *Clinical and Diagnostic Laboratory Immunology* **12**(7), 855–860.
- Hillyer GV, Febo I & Diaz C (2002) The rapid diagnosis of HIV-1 infection in mothers in Puerto Rico: a crucial testing strategy for maximal reduction of perinatal transmission. *Puerto Rico Health Sciences Journal* **21**, 133–135.
- Jamieson DJ, O'Sullivan MJ, Maupin R *et al.* (2003) The challenges of informed consent for rapid HIV testing in labor. *Journal of Women's Health* **12**, 889–895.
- Johnson N, Mullings AA, Harvey KM *et al.* (2004) HIV seroprevalence, uptake of interventions to reduce mother-to-child transmission and birth outcomes in Greater Kingston, Jamaica. *West Indian Medical Journal* **53**, 297–302.
- Knottnerus JA (2002) The evidence base of clinical diagnosis. *BMJ* **324**, 477–480.
- Littenberg B & Moses LE (1993) Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. *Medical Decision Making* **13**, 313–321.
- Liu A, Kilmarx PH, Supawitkul S *et al.* (2003) Rapid whole-blood finger-stick test for HIV antibody: performance and acceptability among women in northern Thailand. *JAIDS: Journal of Acquired Immune Deficiency Syndromes* **33**, 194–198.
- Malonza IM, Richardson BA, Kreiss JK, Bwayo JJ & Stewart GC (2003) The effect of rapid HIV-1 testing on uptake of perinatal

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- HIV-1 interventions: a randomized clinical trial. *AIDS* 17, 113–118.
- Matambo JA, Moodley D & Moodley J (1999) HIV seroprevalence and rapid testing in unbooked pregnant African women. *International Journal of Gynecology and Obstetrics* 66, 289–290.
- Melvin AJ, Alarcon J, Velasquez C *et al.* (2004) Rapid HIV type 1 testing of women presenting in late pregnancy with unknown HIV status in Lima, Peru. *AIDS Research and Human Retroviruses* 20, 1046–1052.
- Minkoff H & O'Sullivan MJ (1998) The case for rapid HIV testing during labor. *Journal of the American Medical Association* 279, 1743–1744.
- Nogueira SA, Lambert JS, Albuquerque AL *et al.* (2001) Assessment of a rapid HIV test strategy during labor: a pilot study from Rio de Janeiro, Brazil. *Journal of Human Virology* 4, 278–282.
- Perez-Then E, Pena R, Tavarez-Rojas M *et al.* (2003) Preventing mother-to-child HIV transmission in a developing country: the Dominican Republic experience. *Journal of Acquired Immune Deficiency Syndromes* 34, 506–511.
- Rajegowda BK, Das BB, Lala R, Rao S & Mc Neeley DF (2000) Expedited human immunodeficiency virus testing of mothers and newborns with unknown HIV status at time of labor and delivery. *Journal of Perinatal Medicine* 28, 458–463.
- Rakgoasi SD (2005) HIV counselling and testing of pregnant women attending antenatal clinics in Botswana 2001. *Journal of Health, Population, and Nutrition* 23, 58–65.
- Rouet F, Ekouevi DK, Inwoley A *et al.* (2004) Field evaluation of a rapid human immunodeficiency virus (HIV) serial serologic testing algorithm for diagnosis and differentiation of HIV type 1 (HIV-1), HIV-2, and dual HIV-1-HIV-2 infections in West African pregnant women. *Journal of Clinical Microbiology* 42, 4147–4153.
- Shankar AV, Pisal H, Patil O *et al.* (2003) Women's acceptability and husband's support of rapid HIV testing of pregnant women in India. *AIDS Care* 15, 871–874.
- Singer DE, Kiwanuka N, Serwadda D *et al.* (2005) Use of stored serum from Uganda for development and evaluation of a human immunodeficiency virus type 1 testing algorithm involving multiple rapid immunoassays. *Journal of Clinical Microbiology* 43, 5312–5315.
- UNAIDS (2004) *Report on the Global AIDS Epidemic*. UNAIDS, Geneva.
- Webber MP, Demas P, Enriquez E *et al.* (2001) Pilot study of expedited HIV-1 testing of women in labor at an inner-city hospital in New York City. *American Journal of Perinatology* 18, 49–57.
- Weber B, Fall EH, Berger A & Doerr HW (1998) Reduction of diagnostic window by new fourth-generation human immunodeficiency virus screening assays. *Journal of Clinical Microbiology* 36, 2235–2239.
- Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM & Kleijnen J (2003) The development of Quadas: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 3, 25.
- WHO (2002) *HIV simple rapid assays: operational characteristics*. World Health Organisation. http://www.who.int/entity/diagnostics_lab/evaluations.
- WHO (2004a) *Rapid HIV tests: guidelines for use in HIV testing and counselling*. World Health Organisation. <http://www.who.int/entity/hiv/pub/vct/en/rapid/hivtests/en.pdf>.
- WHO (2004b) *Prevention of mother-to-child transmission of HIV infection: generic training package*. WHO, Geneva. <http://www.who.int/hiv/pub/mtct/pmtct/en/index.html>.
- Zacharias NM, Athanassaki ID, Sangi-Haghepeykar H & Gardner MO (2004) High false-positive rate of human immunodeficiency virus rapid serum screening in a predominantly hispanic prenatal population. *Journal of Perinatology* 24, 743–747.

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Dépistage rapide du VIH sur le lieu des soins chez les femmes enceintes: une revue systématique et méta analyse

Le dépistage rapide du virus de l'immunodéficience humaine (VIH) sur le lieu des soins a le pouvoir de favoriser les stratégies de prévention de la transmission mère/enfant de l'infection VIH. Les tests rapides ont besoin d'une infrastructure de laboratoire minimale et peuvent être exécutés par le personnel sanitaire avec une formation minimale. Dans notre revue systématique et méta analyse, nous avons pour objectif de résumer la précision globale des tests de diagnostic rapide du VIH dans la grossesse et les résultats tels que l'acceptabilité, la préférence des patientes, la praticabilité et l'impact du test rapide. Nous avons effectué des recherches sur quatre bases de données principales, identifié et examiné 1377 citations et inclus 17 études répondant à nos critères d'éligibilité. Les analyses de ces études ont suggéré une sensibilité et une spécificité globales des tests rapides sur sang plus élevées que celles des tests rapides sur prélèvements oraux. Une stratégie de test en deux étapes, en particulier des tests parallèles, s'est avérée supérieure à la stratégie du test unique sur les lieux de femmes en travail et en accouchement. L'acceptabilité des tests rapides et la préférence des patientes étaient variables selon les études. En général, le test rapide VIH était hautement précis comparé aux tests conventionnels et offre l'avantage clair de permettre l'instauration d'interventions synchronisées pour la réduction de la transmission mère/d'enfant du HIV. Afin d'améliorer la précision du diagnostic et réduire les résultats faux positifs, il pourrait être utile d'effectuer deux tests rapides au cours du travail et de l'accouchement.

mots clés VIH, test rapide, grossesse, criblage périnatal, transmission mère/enfant

Prueba rápida, 'point of care' para VIH en mujeres embarazadas: revisión sistemática y metanálisis

La prueba rápida, 'point of care' para el virus de inmunodeficiencia humana (VIH) en humanos, tiene el potencial de aumentar las estrategias para prevenir la transmisión vertical del VIH. Los pruebas rápidas requieren de una infraestructura de laboratorio mínima y pueden ser realizadas por trabajadores sanitarios con un entrenamiento básico. En nuestra revisión sistemática y metanálisis hemos intentado resumir la precisión diagnóstica global de pruebas rápidas para VIH durante el embarazo, así como resultados tales como la aceptabilidad, las preferencias de los pacientes, la viabilidad y el impacto de realizar pruebas rápidas. Hemos hecho la búsqueda de bibliografía en las cuatro bases de datos principales, identificado y tamizado 1377 citas, e incluido 17 estudios que cumplían con nuestros criterios. Los análisis de estos estudios sugieren que la sensibilidad y especificidad total de la sangre, en pruebas rápidas, era alta comparada con pruebas rápidas orales. Se encontró que, en lugares en donde se atienden partos, la estrategia de realizar las pruebas en dos etapas, particularmente si se realizan en paralelo, es mejor que la de realizar una sola prueba. La aceptación de las pruebas rápidas y la preferencia de los pacientes variaban entre estudios. En general, las pruebas rápidas para VIH eran muy precisas comparadas con pruebas convencionales y ofrecían la clara ventaja de permitir la implementación de intervenciones oportunas para reducir la transmisión vertical de VIH. Con el fin de mejorar la precisión diagnóstica y reducir el número de falsos positivos, podría ser necesario utilizar dos pruebas rápidas al hacerlas a mujeres durante el trabajo de parto y el parto.

palabras clave VIH, prueba rápida, embarazo, tamizaje perinatal, transmisión vertical