ORAL VS. BLOOD BASED HIV POC TESTS: IMPLICATIONS FOR SELF TESTING: A META-ANALYSES

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INTRO

**"There is something better than science- Science with a moral compass.
Science that contributes to social equity.
Science in the service of humanity."**

William Foege, MD MPH
Eradication of small pox

LEARNING OBJECTIVES

A walk through a meta-analyses

Interpreting the maze of fancy HSROC and not so fancy BVR

Predictive values with Bayesian analyses with credible intervals!

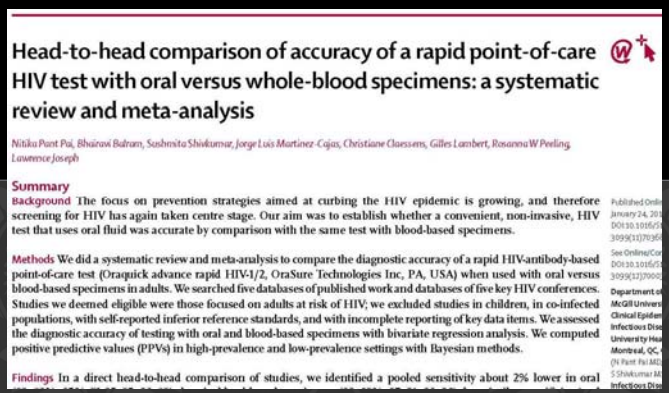
Implications for clinical and public health practice

Caveats of a meta-analyses

Moral of the story

The Story!

THE LANCET Infectious Diseases



Head-to-head comparison of accuracy of a rapid point-of-care HIV test with oral versus whole-blood specimens: a systematic review and meta-analysis

Nitika Pant Pai, Bhairavi Balram, Sasbmita Shivkumar, Jorge Luis Martinez-Cajas, Christiane Claessens, Gilles Lambert, Rosanna W Peeling, Lawrence Joseph

Summary

Background The focus on prevention strategies aimed at curbing the HIV epidemic is growing, and therefore screening for HIV has again taken centre stage. Our aim was to establish whether a convenient, non-invasive, HIV test that uses oral fluid was accurate by comparison with the same test with blood-based specimens.

Methods We did a systematic review and meta-analysis to compare the diagnostic accuracy of a rapid HIV-antibody-based point-of-care test (Oraquick advance rapid HIV-1/2, OraSure Technologies Inc, PA, USA) when used with oral versus blood-based specimens in adults. We searched five databases of published work and databases of five key HIV conferences. Studies we deemed eligible were those focused on adults at risk of HIV; we excluded studies in children, in co-infected populations, with self-reported inferior reference standards, and with incomplete reporting of key data items. We assessed the diagnostic accuracy of testing with oral and blood-based specimens with bivariate regression analysis. We computed positive predictive values (PPVs) in high-prevalence and low-prevalence settings with Bayesian methods.

Findings In a direct head-to-head comparison of studies, we identified a pooled sensitivity about 2% lower in oral

Funding Canadian Institutes for Health Research (CIHR KRS 102067).

www.thelancet.com/infection Published online January 24, 2012 DOI:10.1016/S1473-3099(11)70368-1

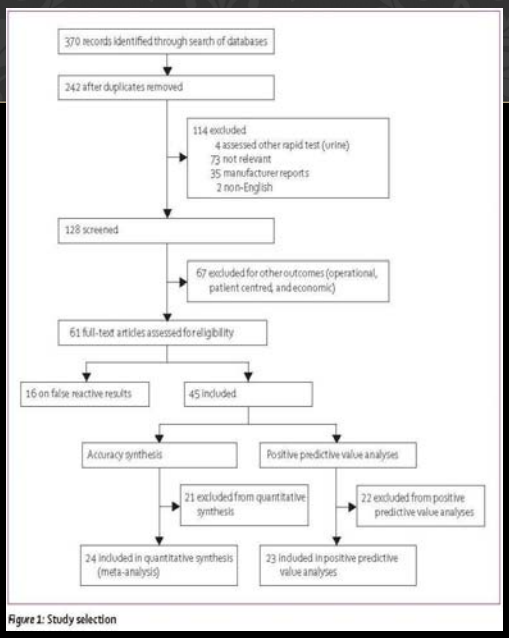


Figure 1: Study selection

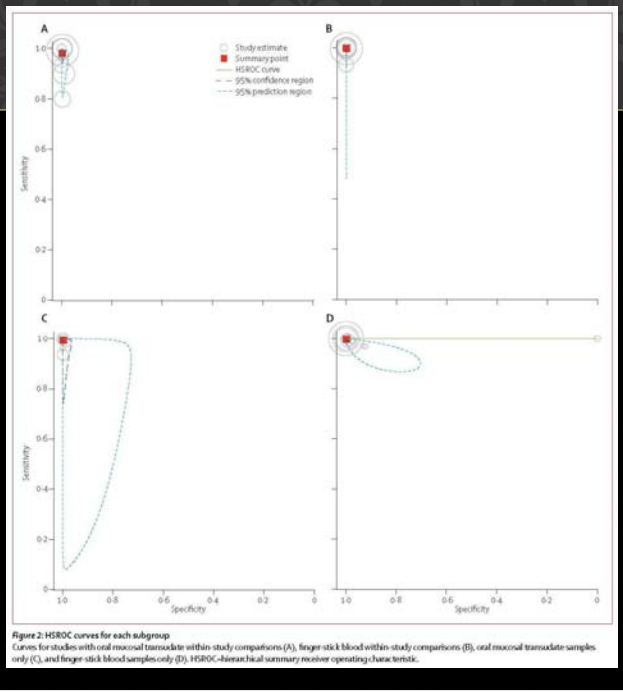


Figure 2: HSROC curves for each subgroup
Curves for studies with oral mucosal transudate within-study comparisons (A), finger-stick blood within-study comparisons (B), oral mucosal transudate samples only (C), and finger-stick blood samples only (D). HSROC=hierarchical summary receiver operating characteristic.

Our first subgroup—the main subgroup of interest— containing studies with both oral and whole-blood comparisons, provided us with the best subgroup for bivariate regression analyses. Pooled sensitivity was greater for whole-blood than oral specimens and pooled specificity was similar for each specimen (table 1). In our second subgroup, studies with no whole-blood comparators, the pooled estimates for sensitivity and specificity were similar to those for whole-blood specimens in our first subgroup; this was also the case in our third subgroup, studies with no oral comparator.

	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Log (diagnostic odds ratio)
Subgroup 1a (oral mucosal transudate within study; n=10)	98·03% (95·85–99·08)	99·74% (99·47–99·88)	383·37 (183·87–799·31)	0·019 (0·009–0·040)	9·87
Subgroup 1b (whole blood within study; n=10)	99·68% (97·31–99·96)	99·91% (99·84–99·95)	1105·16 (633·14–2004·37)	0·003 (0·001–0·034)	12·75
Subgroup 2 (oral mucosal transudate only; n=6)	99·43% (95·28–99·93)	99·86% (99·22–99·98)	721·65 (126·84–4105·76)	0·006 (0·001–0·050)	11·75
Subgroup 3 (whole blood only; n=17)	99·8% (99·07–99·93)	99·78% (99·27–99·93)	466·96 (137·42–1586·76)	0·003 (0·001–0·009)	11·78

n refers to a datapoint (one set of true positive, false positive, false negative, and true negative).

Table 1: **Pooled estimates of accuracy across studies**

DISCUSSION

In our first subgroup, head-to-head comparisons of oral mucosal transudate and finger- stick specimens, the pooled sensitivity of the test in oral specimens was lower than the test's sensitivity in finger-stick specimens, a difference of about 2%. However, the specificity estimates were similar for both specimens. We give greater prominence to this comparison because within-study comparisons reduce confounding present in other subgroups because of different specimens, reference standards, settings, and devices. Six (86%) of seven studies in our first subgroup used what we defined as perfect reference standards, assessing only one device in two specimens (i.e. oral mucosal transudate and finger-stick blood), forming an ideal group for within-study comparisons.

By comparing the pooled estimates from our analyses with the manufacturer's claims (sensitivity 99·3%, 95% CI 98·4–99·7; specificity 99·8%, 99·60–99·89), only the pooled specificity estimates from our study came close to those quoted by the manufacturer. Discrepancy in sensitivity estimates from the manufacturer's estimates could be because the assessments were done in carefully controlled laboratory settings of serum panels. study settings, study designs, populations, prevalence, and variable quality control procedures might affect the diagnostic performance of a test in field assessments. This difference in performance is also referred to as the optimism bias

SECOND OBJECTIVE: PPV AND PREVALENCE!

Evaluating changes in PPV (pooled PPV) in different populations stratified by risk (high vs. low) (surrogates of prevalence)

In two specimen groups (finger stick vs. OMT)

	Positive predictive value (95% credible interval)
Blood group (n=32)	
High-risk populations (n=10)	98·50% (93·10–99·79)
Low-risk populations (n=22)	97·65% (95·48–99·09)
Overall	98·03% (96·38–99·08)
Oral mucosal transudate group (n=31)	
High-risk populations (n=11)	98·65% (85·71–99·94)
Low-risk populations (n=20)	88·55% (77·31–95·87)
Overall	94·88% (87·66–98·4)

n refers to one set of true positives and false positives.

Table 2: Pooled estimates of positive predictive value

By use of Bayesian hierarchical meta-analytic models, we obtained estimates of PPVs for whole-blood and oral specimens in high-prevalence and low-prevalence settings.

Point estimates and 95% credible intervals for PPV provided similar estimates for blood and oral specimens in high-prevalence settings

By contrast, in low prevalence settings, PPV estimates were higher for blood than oral specimens.

To put our findings in context,

the lower sensitivity of the test in oral mucosal transudate compared with blood specimens is probably because of a lower quantity of HIV antibodies in oral mucosal transudate than in whole blood.

The titre of HIV antibodies is also low in acute HIV infection before seroconversion, hence the increased possibility that oral testing might miss more acute HIV infections than tests with blood specimens because of its lower sensitivity. Although a very high or perfect (100%) sensitivity is desirable, it is difficult to achieve.

HIV public health programs should emphasize this fact before recommending the oral test as a first-line screening test to detect early HIV infection in settings with low HIV prevalence.

The inability of the test to identify infection during the window period must also be emphasized. Nucleic acid amplification testing and antigen antibody combination rapid tests identify infections missed by antibody-based tests..

To put our findings into context,

Therefore, for self-testing initiatives, if the self perception of risk of a potential test taker is high, or if they suspect recent exposure to HIV and are within the window period, but their self-test result shows up as negative with an antibody based self-test, they should be actively encouraged to seek further confirmatory testing with advanced tests immediately at a referral centre of choice.

Discussion and implications...

As our second objective we assessed the effect of surrogate prevalence estimates of HIV obtained with seropositivity estimates from each study, and their effect on PPVs.

In this analysis, we noted that although the performance of the test in blood and oral specimens was similar in settings of high prevalence, the lower end of the 95% credible intervals was slightly lower for oral than for blood specimens (85·71% vs 93·10%; table 2).

This variability is important to keep in mind when rolling out oral tests for expanded HIV-testing initiatives. Further, in low-prevalence settings, the test was inferior in oral compared with blood specimens.

For this PPV analysis we excluded assessments in laboratory settings and case-control designs, and focused solely on implementation research data that related to real-life settings.

the PPV of a test is a function of the prevalence of the disease in the population, lower PPV is attributable to a large number of false positive results compared with true positive results. Subsequently, the large variability in PPV in low-prevalence settings where oral specimens were assessed implied the possibility of missing detection of new infections in settings of low prevalence and in populations at low risk of HIV acquisition.

These data corroborated the data on pooled accuracy (table 1), where negative likelihood ratios were small and similar, but positive likelihood ratios differed.

To put this in context, although the oral test is popular because of its convenience and ease of specimen collection, compared with the blood-based test, the use of a single oral test in low-prevalence settings could lead to a higher number of false positives than blood-based testing. This problem could be compounded in national screening program and needs to be considered in the widespread implementation of HIV testing, including home-based testing, self-testing, or over-the-counter testing initiatives, in all low-prevalence settings.

CAVEATS

- Predictive values are not intrinsic attributes of a diagnostic test and are highly dependent on the prevalence of target disease.
- Further, a meta-analysis is used to estimate the group mean under the assumption that samples in individual studies were taken from the same population, when heterogeneity is not excessive as is evident in our meta-analysis, where homogenous subgroups were created to assess accuracy based on specimens.

- Oraquick is a diagnostic device and its performance varies with host response to HIV.
- biological variations in host responses as well as immunological responses take time
- window period to allow for seroconversion.
- Although the test's sensitivity seems to be lower with oral versus blood specimens, both estimates obtained in our meta-analysis were at the extreme upper end of the range and there is a great deal of overlap in Cis.
- we could argue that the robustness of the difference is uncertain and might be affected by the results of one or two studies.

- The clinical significance of this difference might also be overshadowed by intrinsic variability in host status and time of testing relative to exposure—something we cannot rule out with our present analysis.
- Most data in our meta-analysis were reported from a high-income setting like the USA, whereas the rest of the data were from well controlled studies in developing settings. These data might not be representative of routine services in less developed countries.
- Finally, our review focused on Oraquick, the only FDA approved Clinical Laboratory Improvement Amendments waived test with enough worldwide data for a comparative meta-analyses.
- The only other test available in an oral format is Aware HIV-1/2 OMT (Calypte Biomedical Corporation, Portland, OR, USA); an over-the-counter non-FDA approved version is available on the market. This test has restricted blood versus oral comparative and independently assessed worldwide data, hence our focus on Oraquick.

- Our meta-analysis has a potential for biases: detection, partial verification, and publication bias.
- Because of restricted data in each subgroup, we could not explore the role of study designs, treated versus untreated HIV infection, and reference standards in diagnostic accuracy assessments.
- Additionally, because of a lack of data on true-negative and false-negative values required for negative predictive value calculations, we were unable to explore changes in negative predictive value and PPV with changes in prevalence or apply the estimated likelihood ratios and sensitivity and specificity to the full range of prevalence and plot them in a suitable graph.
- Lastly, the lack of independently assessed comparative worldwide data on Aware HIV-1/2 OMT prevented us from assessing it in our meta-analyses.

CONCLUSION

In this first Bayesian comparative meta-analysis of worldwide diagnostic performance data, we conclude that oral Oraquick had lower sensitivity but similar specificity to Oraquick with whole-blood specimens. Although we identified high PPVs for both oral and blood specimens in high-prevalence settings, we obtained a low PPV with oral specimens for low-prevalence settings.

PRESS

HUFF POST BLACKVOICES CANADA

Saliva HIV Test As Effective As Blood Test: Study

First Posted: 01/30/2012 3:12 pm Updated: 01/30/2012 3:58 pm

Despite advances in the treatment of HIV, one huge challenge still lingers in the medical community: getting people tested in

The stigma associated with being tested and potentially exposed in a public clinic has prompted scientists at the Research Inst University Health Centre to evaluate the efficacy of an oral HIV self-test, a method they believe can serve as an effective but alternative to clinical testing.

Compared to a traditional blood screening, the saliva test OraQuick HIV1/2, the only oral fluid test approved for use in a heal Food and Drug Administration, was 99 percent accurate in detecting HIV antibodies in high-risk populations and about 97 pe populations, according to study findings published in the journal *The Lancet Infectious Diseases*.

To evaluate this saliva test's potential for worldwide use, researchers analyzed real-life field research data from five global da groups include injection drug users, men who have sex with men, and people who have unprotected sex

TheScientist
MAGAZINE OF THE LIFE SCIENCES

Saliva Legit for HIV Testing

A quick spit test is as good as blood for detecting HIV, and could encourage self-testing initiatives in the US and Africa.

By Megan Scudellari | January 25, 2012

OraQuick HIV test

A pain-free, non-invasive saliva test is as accurate as a traditional blood test to diagnose infections of the human immunodeficiency virus (HIV), according to a new meta-analysis published yesterday (January 24) in *The Lancet Infectious Diseases*. The test could be a solution for countries that wish to adopt self-testing strategies for HIV.

Pooling data from five worldwide databases, an international team of researchers found that Oraquick HIV-1/2, a saliva test sold by Pennsylvania-based OraSure

THE TIMES OF INDIA Health & Fitness

Saliva HIV test as accurate as blood screening

ANI Jan 25, 2012, 05.36PM IST

Tags: saliva test | saliva | McGill University | HIV

Researchers including one of an Indian origin have revealed that saliva test used to diagnose the human immunodeficiency virus (HIV), is comparable in accuracy to the traditional blood test.

A new study led by the Research Institute of the McGill University Health Centre (RI-MUHC) and McGill University found that the saliva HIV test, OraQuick HIV1/2, had the same accuracy as the blood test for high-risk populations.

0

Recommend

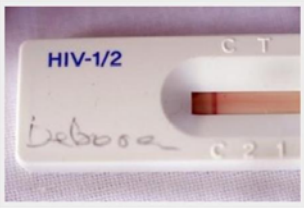
(Saliva HIV test as accurate as blood screening (Thinkstock photos/Getty Images))

Times LIVE

Home › HIV Special Report › Article ›

Oral HIV test results found to be less reliable

HARRIET MCLEA | 24 January, 2012 00:22



A new study on oral HIV tests has added fire to the debate on whether self-testing should be allowed in South Africa.

A NEW study on oral HIV tests has added fire to the debate on whether self-testing should be allowed in South Africa.

The study, which compared the accuracy of testing for HIV using cheek and gum tissue (oral mucosal transudate) to blood tests, was

ECKHART TOLLE

Some changes look negative on the surface but you will soon realize that space is being created in your life for something new to emerge.

**

Realize deeply that the PRESENT MOMENT is all you have.

Make the NOW the primary focus of your life.

***

Whatever you fight, you strengthen, and what you resist, persists.

***

ET!