

Diagnosing HIV: oral fluid HIV tests – diagnostic accuracy and patient acceptability

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• Executive summary/Key messages

In operational conditions in resource poor settings, rapid, point of care, oral fluid HIV tests have not been found to be sufficiently accurate to be used as the sole means of HIV diagnosis.

No rapid, point of care, urine HIV test has been evaluated.

Sparse evidence suggests that oral fluid tests are more popular with patients than urine or serum tests and that oral fluid tests do not appear to confuse the message about HIV transmission.

It is not known how people's knowledge and beliefs of HIV transmission in such settings will impact on their choice of test, but having an oral fluid test may improve their understanding of HIV transmission routes.

There is no evidence as to whether rapid oral tests improve uptake of HIV testing in resource poor settings.

Further studies in resource poor settings are required. These should be designed such that they compare oral (or urine when available) based rapid tests with serum based rapid tests. The outcomes to measure include: rate of test uptake and receipt of results, the time taken processing the tests, what patients' views are about the test collection method, and how the means of testing affects patient understanding of HIV transmission.

Until then oral fluid tests should only be used alongside established rapid serum or enzyme linked immunosorbent assay test (ELISA) tests.

• Introduction

Knowledge of HIV status is pivotal to HIV prevention and access to care. One factor that contributes to improving the rates of testing and patients receiving their test results is the nature of the test itself. Rapid (take less than 30 minutes to process), serum based point of care diagnostic tests that can be read visually have been found to increase the proportion of patients being counselled after testing and receiving their results in settings such as Kenya and Uganda, and in Zambia where patients reported a preference for same day results.[1][2][3] Advantages over conventional serum enzyme linked immunosorbent assay test (ELISA) tests have been described: rapid tests allow decentralisation of testing services as there is no requirement for instruments or reagents and no reliance on infrastructure (and electricity). Rapid tests are also simpler to use and interpret (less training required), have a longer shelf life, are robust (can be stored at 4–33 °C), include an internal control to minimise false negatives, and enable flexibility with the number of

tests performed.[4] They are also more acceptable to patients and healthcare staff (decreased risk of occupational exposure compared with venepuncture).[5]

Laboratory based serological HIV assays using oral fluid or urine have also been developed. They detect immunoglobulin G (IgG), present in much smaller quantities than in plasma, and have a high sensitivity and specificity. The accuracies of these have been validated in several resource rich and resource poor settings.[6] [7]

Point of care tests that use oral fluid (often referred to as saliva tests) have now been developed, but less is known about their accuracy and acceptability in operational conditions in resource poor settings. They are likely to bring advantages in such settings: decreased risk of transmission of blood borne infection (by needle stick); no requirement of healthcare workers (or volunteers) for certification to work with exposure prone procedures; no requirement for sterile needles, syringes, or gloves or their safe disposal; increased patient acceptability (less discomfort, reduced fear of infection with poorly sterilised needles). The test may be easier for the healthcare worker to perform (e.g. in an obese patient or intravenous drug user).[4]

However, oral fluid tests may bring new problems such as confusion about transmission routes, for example, “if you test saliva the virus must be in saliva”, with consequent misunderstandings about the safety of kissing or sharing meals. There is also a theoretical risk of transmission of respiratory pathogens such as tuberculosis, and the significance of oral disease in influencing the test efficacy needs evaluating.[8] Furthermore, despite oral fluids being easier to collect, some oral fluid based tests may involve more complex or additional steps to process.[9] [10]

We set out to find the evidence for the accuracy and acceptability of rapid, point of care, oral or urine based tests for the diagnosis of HIV in resource poor settings.

• **Synthesis of current guidelines**

No guideline exists on the use of rapid oral fluid or urine tests in resource poor settings. WHO has issued guidelines for rapid tests, but although the document acknowledges rapid oral fluid and urine tests it makes no further recommendation stating that “although rapid HIV tests have been developed which use saliva and urine, this document concentrates on tests involving the use of whole blood, serum, or plasma”. [5]

Guidelines from resource rich settings are available. In the USA, the Centers for Disease Control and Prevention’s guidelines for oral rapid tests are the same as for non-oral rapid tests: any reactive rapid test must be followed up with a western blot or immunofluorescence assay.[11] This guidance allows for the fact that low prevalence of HIV in the general population in this setting means that false positive results are likely, whereas false negative results are a rarity.

The guidelines set out the characteristics required of a rapid test (see table 1) and the algorithms to use for confirmatory testing.

Table 1: Summary of characteristics of rapid HIV tests for testing and counselling programmes.[5]

<p>Accuracy High sensitivity > 99% High specificity > 99% High reproducibility* > 98%</p> <p>Specimen type Preferably for use on whole blood (finger prick samples) for ease of collection and to avoid the need for centrifugation</p> <p>Small amount of laboratory equipment required</p> <p>No constant electricity or water supply required</p> <p>Easy to perform Little technical training required Few steps</p> <p>Easy to interpret Visual interpretation of results, usually without equipment Stable reading endpoint Rapid < 30 minutes</p> <p>Easy to store Storage at room temperature for several weeks (provided there are no significant temperature fluctuations) Shelf life ≥ 12 months</p> <p>Number of tests performed Suitable for individual and small volume testing, e.g. 1–40 samples per day</p> <p>Minimal waste and waste disposal</p> <p>Low cost at about < \$1.0 for the initial screening</p> <p>* Reproducibility, expressed as a percentage, is calculated by dividing the number of concordant results by the total number of samples retested.</p>

In settings with a low level HIV epidemic (HIV prevalence has not consistently exceeded 5% in any defined subpopulation), tests with a sensitivity or specificity greater than 99% should be used in order to achieve satisfactory positive predictive values.

- **WHO technology appraisals of efficacy of rapid oral fluid tests**

WHO has performed a laboratory based technology appraisal on three rapid, point of care, oral fluid tests: OraScreen HIV Rapid Test (Beacon Diagnostics, Hayward, CA, USA), Salivax-HIV (ImmunoScience, Inc, Pleasanton, CA, USA), and SMLX Technologies Diagnostics Test (SMLX Technologies).[9] A total of 222 oral fluid specimens were collected using the collecting devices supplied with the test kit and 75 samples were HIV positive. Although it rated all three as suitable for small laboratory use and easy to use, the sensitivity and specificity were poor compared with a reference enzyme linked immunosorbent assay test (ELISA) laboratory based salivary test (Wellcozyme HIV 1+2 GACELISA, Murex Diagnostics, Dartford, UK) or matched serum tests (see table 2)

Table 2: Sensitivity and specificity of rapid oral fluid tests.[9]

	OraScreen HIV Rapid Test	Salivax-HIV	SMLX Technologies Diagnostics Test
Sensitivity (95% CI) 75 samples	56% (44% to 68%)	79% (67% to 89%)	63% (51% to 74%)
Specificity (95% CI) 147 samples	99% (95% to 100%)	96% (91% to 99%)	75% (67% to 82%)

WHO has also recently performed a laboratory based technology appraisal on another rapid, point of care, oral test (OraQuick Rapid HIV-1/2). However, efficacy was tested using an evaluation panel of serum specimens rather than oral fluid. There was an overall sensitivity of 98.1% (95% CI 94.5 to 99.6) and specificity of 100.0% (98.8% to 100.0%). It was rated as 10/10 by the technology appraisal, “very easy” (score 30/30) for ease of use, and “very suitable” (34/40) for suitability for

use in a small laboratory. As the kit was not tested with oral fluid samples in this analysis, these results cannot be extrapolated to predict how effective the kit would be when using actual oral fluids.[10]

The Food and Drug Administration (FDA) has recently also approved OraQuick Rapid HIV-1/2. The product insert reports from the manufacturer's own trials (using oral fluid) a sensitivity of 99.3% (95%CI 98.4% to 99.7%; 3917 people) and specificity of 99.8% (95% CI 99.6% to 99.9%; 3755 people). The study included an additional group who were known to be HIV positive for the sensitivity but not specificity analysis.[12]

• **Key questions relevant to resource poor settings:**

What is the diagnostic accuracy of rapid, point of care, oral or urine based tests compared with reference standards?

Are oral or urine HIV tests more acceptable to patients than serum based tests?

• **Methods**

The search was undertaken in April 2006. The following sources were searched for systematic reviews, RCTs, and observational studies: Medline, Embase, The Cochrane Library, Central, Database of Reviews of Effects, HTA Database, Trip Database, AIDsearch, African Journals Online, African Index Medicus, Global Index Medicus, Lilacs, and Index Medicus for South East Asia Region. Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies, and then sent to the author for further assessment of the full articles.

The author included studies that were from resource poor settings, presented sensitivity and specificity data, and compared surrogate markers: WHO clinical stage (WCS); TLC at specified cut-off points; change in TLC from baseline if monitoring therapy or composites of clinical staging and laboratory indices against a reference standard of either: CD4 alone with a 200 or 350 cells/mm³ cut-off, CD4 count in combination with clinical stage, or CD4 change from baseline if monitoring therapy.

Studies from resource rich settings were only included when we found no corresponding study from a resource poor setting.

Total lymphocyte counts have been recorded as $\times 10^9$ cells/L and CD4 counts as cells/mm³ in the text.

• **Outcomes**

Sensitivity, specificity, patient acceptability.

What is the diagnostic accuracy of rapid, point of care, oral or urine based tests compared with reference standards?

Introduction

Laboratory based blood, urine, and oral fluid based assays for HIV have been in use for up to 10 years worldwide. Rapid, point of care, blood based assays have been developed and are now widely used. Recently, similar devices for rapid point of care testing of oral fluid have been produced. We included any study from a resource poor setting that compared rapid oral or urine tests against a reference standard where the test was collected and read at the point of care (i.e. the collected sample was not stored then transported to a laboratory for analysis). We found no studies of rapid point of care urine tests.

Evidence summary

We found five studies performed in resource poor settings, one in India and four in Africa (see table 3). All found that, compared with reference tests, oral fluid tests had sensitivity ranging from 75% to 94% and specificity ranging from 97% to 100%. This does not meet the WHO recommendations that tests have 99% or greater sensitivity and specificity.

Evidence from resource poor settings

RCTs

No RCTs were found.

Point of care diagnostic accuracy studies

Three studies used the same oral fluid test (OraQuick Rapid HIV-1/2; OraSure Technologies Inc, Bethlehem, PA, USA). One evaluated Salivax-HIV and one assessed Orapette SalivaCard HIV-1/HIV-2 (Trinity Biotech, Bray, Co Wicklow, Ireland).

OraQuick Rapid HIV-1/2

We found three studies that compared OraQuick Rapid HIV-1/2 versus reference standard (see table 3).[13][14][15] The first study, performed on 1244 women in an antenatal setting in India, found a sensitivity of 75% but specificity of 100% compared with reference standard. In a parallel arm of the study, using finger prick blood specimens from the same participants, the sensitivity improved to 86.4%.[13] The second study tested 377 adult inpatients (all suspected of having tuberculosis) in two central hospitals in Botswana. Sensitivity was 98.4% and specificity was 98.3% compared with reference standard.[14] The third study tested 235 children born to HIV positive women in South Africa. The sensitivity was 87% and specificity 97% compared with reference standard. Median age was 12.1 months with a range from 11 months to 18 months. The reference standard was two negative serum enzyme linked immunosorbent assay test (ELISA) tests at 18 months to confirm true negative and HIV DNA PCR + clinical evaluation for true positives. Given the particular nature of the HIV/immune system interaction in this age group the results of this study cannot be generalised to older children or adults.[15]

Salivax-HIV

We found one study of 200 people in Nigeria that compared the Salivax-HIV oral test performed at point of care with matched serum using two rapid EIA tests.[16] Sensitivity was 94% with specificity of 100% (see table 3).

Orapette SalivaCard HIV-1/HIV-2

We found one study in Nigeria where Orapette SalivaCard HIV-1/HIV-2, another rapid oral test, was evaluated under routine conditions in 150 people.[17] Sensitivity of 79.7% and specificity of 97.8% were found to be poor compared with reference standard. Data were taken from abstract as full paper was unavailable; it is unclear if study was performed under operational conditions.

Laboratory based diagnostic accuracy tests

OraScreen HIV Rapid Test

Another rapid test, OraScreen HIV Rapid Test was evaluated in a laboratory setting in the resource poor setting of Jamaica, using serum and saliva samples obtained from 257 volunteers from a family planning clinic and from visa applicants (representing what was perceived as a low risk population) and from 52 volunteers known to be HIV infected.[18] It found sensitivity and specificity of 100% compared with matched sera tested with enzyme linked immunoassay and Western Blot. However, one person who was HIV positive was unable to produce enough oral fluid for the test. Although this was a point of care test, the analysis was carried out in a separate laboratory on frozen oral specimens and, thus, does not reflect operational conditions. The study was funded by the test kit manufacturer.

Comment

WHO guidelines for HIV testing advocate the use of multiple assays (at least 1 screening and 1 confirmatory) in algorithms to maximise the accuracy of the test, unless the first test is negative. The rapid tests that can be obtained through the WHO bulk procurement scheme have to meet preset criteria with “levels of sensitivity and specificity greater than or equal to 99%”. [5]

Of the studies undertaken in operational conditions, none of the evaluations found a sensitivity of 99% or greater. The largest study performed in a setting most similar to those where such rapid oral testing might be employed had a sensitivity of 75%. [13]

Each test makes claims of high (> 99%) sensitivity and specificity in package insert data. [12] [19] Studies in resource rich settings have found higher sensitivity and specificity for OraQuick Rapid HIV-1/2 (sensitivity 100%, specificity 96%) [20] and Orapette SalivaCard HIV-1/HIV-2 (sensitivity 100% specificity 99.8%), [21] although the SalivaCard study was not conducted under operational conditions.

However, results from the WHO test panel, despite the tests being performed under optimal laboratory conditions, were not encouraging for three tests. The fourth test, OraQuick Rapid HIV-1/2 has not yet been evaluated by WHO with oral fluid. [9]

On the basis of these findings a confirmatory test would be necessary for HIV negative as well as HIV positive results if these rapid, oral fluid assays were used in a diagnostic HIV setting (rather than for surveillance). In settings with high HIV prevalence, high positive predictive values may still be achieved, but WHO guidelines would nevertheless advocate confirmation of any positive test. The low negative predictive value, in high prevalence settings, given the sensitivities described above would also necessitate confirmatory testing. Such a negative confirmatory test would need a high sensitivity, which on current evidence could not be a second rapid oral test, but would need to

be a serum based rapid test or laboratory based oral fluid ELISA. As such the full advantages of rapid oral testing could not be realised.

In conclusion, the evidence found suggest the rapid oral fluid tests are not sufficiently accurate in operational circumstances to be the sole means of testing. However, the data were sparse. We found no studies of rapid, point of care, urine based HIV tests. Further studies of rapid oral fluid and urine tests are required, preferably studies performed in a variety of settings and geographical situations. It would also be valuable for them to assess a confirmatory strategy.

Are oral or urine HIV tests more acceptable to patients than serum based tests?

The effectiveness of the test will also depend on its acceptability among those candidates for testing. We looked for any study that assessed the uptake of testing and the proportion of people who received the result with any oral or urine based test versus tests requiring blood (either finger prick or venepuncture). Studies that reported qualitative data from patient interview were also included.

Evidence from resource poor settings

RCTs

We found no RCTs.

Observational studies

We found four studies, one undertaken in Brazil and the others in Africa. Three studies found that non-invasive oral fluid or urine HIV tests were more popular than invasive tests. However, in two of these studies, the findings were from post hoc analysis and had not been the primary focus of the trial, while the third asked participants who had already agreed to having both a serum and oral fluid test. None of the studies assessed what proportion of people returned to receive test results. One study in Uganda found that people *do* think that oral fluid could be a route of HIV transmission, but having an oral fluid based test decreased rather than increased the prevalence of this belief. No study has assessed whether such beliefs affect acceptance of oral fluid testing.

In Tanzania, 325 people were recruited from an HIV clinic (135 known HIV positive patients), a voluntary counselling, and a testing centre and hospital ward in a study of the acceptability and accuracy of a laboratory based, oral fluid based assay. All those recruited had venepuncture and oral fluid collected. Sixty-five per cent preferred oral fluid collection, 23% preferred serum, and 12% preferred urine collection when asked about methods of HIV testing. Overall, 158 (49%) were HIV positive.[22] People in the study already knew their HIV status so effects of testing on the proportion of people who received test results could not be assessed.

Investigators in Brazil offered saliva screening of 331 children (mean age 38 months, all born to HIV positive mothers, all of whom had previously had serum testing) to their parents/guardians. The uptake of the two tests types was 91%, but a further 6% who originally declined blood screening accepted saliva testing.[23] This comparison was not part of the original trial design, but a post hoc analysis. All children attended follow up at the clinic; however, the study did not report what proportion of children received their oral fluid test results.

In Uganda in a trial focusing on sexually transmitted disease control, participants were screened for HIV with blood and urine tests.[24] The uptake of both was high, but greater for urine (95%) than blood (90.5%). This was a study of anonymous HIV screening. Results for the proportion of people with HIV who received their results were not reported.

A fourth study (502 people) was designed to assess beliefs about HIV transmission, First time STD clinic attendees in Uganda were interviewed before and after being offered both serum and oral fluid testing for HIV in a study that was also comparing test accuracy of a laboratory based oral fluid assay (50% were male, the mean age was 26 years, and 41% were subsequently found to be HIV positive).[25] Participants were asked whether a mode of transmission was very unlikely, possible, or very likely. Ninety-nine per cent were aware that HIV transmission was very unlikely when shaking hands but very likely through sexual intercourse. Transmission risk by oral fluid was less well understood. 87% of people believed that sharing a straw, 35% that sharing a toothbrush, and 69% that kissing mouth to mouth were very unlikely means of transmission. Most of the remainder thought these routes were possible rather than they were very likely. After counselling and collecting the oral fluid and serum (but before the results were available) significantly ($P < 0.0001$) fewer people thought oral fluid transmission of HIV was possible, but more than two thirds had still not changed their belief. Generalisation from this study may be limited as it was conducted in an urban population in 1993. It is possible that understanding of HIV has changed since, and may be different in rural populations.

Comment

Another qualitative study has also shown that, while rapid oral tests were popular, people receiving voluntary counselling and testing expressed confusion about the mode of transmission. The study concluded that counselling and education should provide an accessible explanation of the distinction between oral transmission and oral testing.[26] This study has not been peer reviewed. Evidence from resource rich settings is available with similar findings. Saliva testing has been shown to be more acceptable than serum testing in studies in the UK and USA among prostitutes, intravenous drug users, homosexual men, and in prisoners.[27][28][29][30] A study of adolescents in the USA found oral tests were preferred to urine or blood tests, and rapid to non-rapid tests, the most favoured being a rapid oral fluid test.[31]

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Table 3: Point of care diagnostic accuracy studies in resource poor settings							
Ref	Population	Intervention	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Comments
[13]	1244 women from Pune, India, 3% HIV positive	OraQuick Rapid HIV-1/2 test v EIA and WB	75%	100%	100%	9.1%	Women presenting for first antenatal visit with unknown HIV status. Saliva, finger prick (tested at POC), and venepuncture samples. Serum had higher sensitivity of 86.4%. HIV status not known to those reading test
[14]	377 adult inpatients from Botswana, 84% HIV positive	OraQuick Rapid HIV-1/2 test v two ELISA tests with WB for resolving discordant results	98.4% (95% CI 96.5% to 99.4%)	98.3% (95% CI 91.9% to 99.9%)	99.7% (95% CI 98.4% to 100.0%)	92.1% (95% CI 83.3% to 97.0%)	Adult inpatient tuberculosis suspects at central referral hospitals with unknown HIV status. POC test was performed on gingival swabs and compared with collected and stored sputa and sera. HIV status not known to those reading test
[15]	235 children from South Africa, 11% HIV positive	OraQuick Rapid HIV-1/2 test v HIV DNA PCR plus clinical assessment	87%	97%	68%	99.1%	Children (born to HIV positive mothers) attending PMTCT clinic tested with POC oral fluid test. Median age 12.1 months (range 11 months to 18 months). Aim of study was to test specificity. Children still had maternal antibody on ELISA. Observer blinded to HIV status
[16]	200 people from Nigeria, 103/200 (52%) HIV positive	Salivax-HIV v two rapid EIA (Immunocomb HIV 1&2 [AMS, Bucharest, Romania] and Genscreen HIV 1&2 [Bio-Rad Laboratories, Marnes-la-Coquette, France])	97/103 (94%)	97/97 (100%)	NR	NR	100 known HIV patients from ARV clinic and 100 blood donors. False negatives were all asymptomatic HIV with CD4 > 500 cells/mm ³
[17]	150	Orapette	79.7%	97.8%	67.8%	NR	50 people known

	people from Nigeria, 59/150 (39%) HIV positive	SalivaCard HIV-1/HIV-2 v Novopath HIV Immunoblot [Bio-Rad Laboratories, Marnes la Coquette, France]					HIV and 100 people of unknown status Data available only from abstract; unclear if this was performed under operational conditions
ARV, antiretroviral; EIA, enzyme linked immunoassay; ELISA, enzyme linked immunosorbent assay test; PCR, polymerase chain reaction; PMTCT, preventing mother to child transmission; POC, point of care; WB, Western Blot; Ref, reference.							