Acceptability, feasibility, and impact of introducing the rapid oral test in the CBVCT services network

Study Report WP8

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The document “Acceptability, feasibility, and impact of introducing the rapid oral test in the CBVCT network” has been developed through the contribution and expertise of a number of different people within the project “HIV community-based testing practices in Europe” (HIV-COBATEST) with co-funding from the Executive Agency for Health and Consumers (EAHC) under the EU Public Health Programme (Grant Agreement N° 2009 12 11).

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1. Background

Rapid HIV tests can play an important role in HIV prevention activities and expand access to testing in both clinical and nonclinical settings. They can help overcome some of the barriers to early diagnosis and improve linkage to care of infected persons[1]. In the last years some rapid HIV tests have been commercialized. All of them are screening tests that require confirmation if reactive. The procedure is very easy and requires no instrumentation. The results are interpreted visually and are available in few minutes; this is an important fact that allows tested persons to know it on the same day preventing "lost to follow up".

Use of oral specimens, instead of blood specimens, offers some benefits for HIV testing outside health care settings and laboratories, in point-of-care settings: is a non-invasive method, can be performed almost anywhere, and reduce risks of manipulating biological materials and wastes.

In 2004, OraQuick Advance received the US Food and drug Administration (FDA) approval for use with oral fluid and for detection of both HIV-1 and HIV-2[2]. In 2007 the test received the CE mark required for its commercialisation in the European Union[3]. This test can be used also with a finger prick blood specimen.

OraQuick test has been used in several scenarios in United States, including labour and delivery rooms, emergency departments, outpatient clinics, services to inpatients, prisons and occupational exposures. The test has been also used in outreach programs, community-based services and in Voluntary Counselling and Testing sites.

Several studies have shown good accuracy of the test in many scenarios, demonstrating sensitivity and specificity average values of 100% and 99.8% respectively[4-11] (see annex 1). However, in December 2005, and most recently in late 2007, unusually high rates of false-positives results with the oral fluid-based OraQuick test were reported in some U.S. cities[12,13]. The field investigation conducted did not suggest a specific cause for the cluster, and the subsequent incidence study detected no false-positive tests[6,12,13]. The specificity of the test during that period was between 98.9% and 99.5%, always above the minimum threshold of specificity recommended by FDA for rapid tests (98,0%)[12,13].

As the test becomes widely used in settings with low HIV infection prevalence, false-positive results may occur. For that reason, following the recommendations of the CDC[12], in order to ensure specificity of OraQuick® Rapid HIV-1/2 Antibody Test and to minimize the adverse effects of false-positive result on both patients and staff, in Work Package (WP) 8 of HIV-

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COBATEST project, all reactive individuals will be also tested using a second OraQuick test on finger-stick whole-blood specimen. The rapid blood test, which uses blood collected from a "finger stick," has a higher specificity. Nevertheless, all reactive results should not be considered definitive. Independently of the result of eventual second rapid test, the patient will be referred to health care system for confirmation, using standard procedures.

This strategy, repeating a rapid test on finger-stick whole blood after receiving a reactive oral fluid test result, allows counsellors to provide more accurate test-result information to patients while minimizing the number of finger-stick tests that must be performed[12].

Differently to USA where the oral test has been used for several years, the implementation of oral rapid test in Europe has been scarce, because the OraQuick wasn't commercialized in Europe until 2007.

A study conducted in genitourinary medicine (GUM) clinics in London, with an HIV prevalence of 5.73%, showed a sensitivity of 93.64% (95% CI: 82.46-98.66%) and a specificity of 99.87% (95% CI: 99.28%-100%)[8]. Three false positives were found, but were attributed to reading errors. If we don't take into account these errors, then the sensitivity increases to 100%.

Other studies analyze the acceptability of oral test in different scenarios. Studies performed in U.S. have shown rapid tests have good acceptance for patients attending Emergency Departments and patients attending community-based Voluntary Counselling and Testing sites[14-16]. Another study conducted in UK, analyzed acceptability and viability of offering oral test to Primary Health patients, concluding that was viable and could be an effective measure to increase HIV testing rates in Primary Health Care[17].

A study performed by the main partner showed that the introduction of rapid HIV testing in the VCT network of Catalonia has resulted in a large increase in the number of tests performed in these centers (102.9%) in a year[18]. In a previous study in the New York State Anonymous HIV Counselling and Testing Program, there was an increase of 36% in the number of tests performed 6 months after the introduction of the rapid test[19]. Another study, conducted in genitourinary medicine (GUM) clinics in London, showed that patients at high risk of HIV and refusing standard HIV testing may be more likely to accept HIV testing if offered a rapid test[20]. Based on all these facts, an increase of the number of tests performed on the services participating at the network is expected after the implementation of oral rapid tests.

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2. Objectives

- The objective of the study was to assess the acceptability, feasibility and potential impact of introducing oral rapid test technologies at CBVCT.

3. Methodology

3.1. Training in the use of OraQuick test

Before starting the study, a workshop for training in the use of OraQuick test was held in Barcelona. One CBVCT service representative from each participating country attended this workshop. Each CBVCT service trained representative was responsible of the training of the rest of his/her CBVCT service colleagues.

All participating CBVCT services had to promote the study among their clients before its beginning.

The specific objectives of the workshop were:

- To review the usefulness of oral rapid test
- To learn about the use of oral rapid test
- To practice in the use of oral rapid tests

The agenda for the workshop was:

- Background
    - The state of the art of HIV diagnostic tests
    - OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test
        - Biological principles of the test
        - Performance of the test
    - Literature review about OraQuick
- Practice part
    - General tests preparation
    - Testing procedure
    - Interpretation of test results
    - Quality control assessment
    - Practice session with the test

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3.2. Study sites

10 CBVCT services members of the European Network of CBVCT services established by the WP7, from 9 different countries participated in the study:

- BCNCheckpoint-Hispanosida (Spain)
- AIDES (France): 5 regions: Rhône-Alpes, Aquitaine, Saint-Martin, Clermont-Ferrand and Paris's region
- STOP AIDS (Denmark)
- LEGEBITRA (Slovenia)
- AIDS-Hilfe (Germany): AIDS-Hilfe Bochum e.V. , AIDS-Hilfe Hagen e.V.
- Czech Aids Help Society (Czech Republic)
- National AIDS Centre (Poland): CBVCT centre in Warsow and CBVCT centre in Wroclaw.
- ARAS (Romania)
- Checkpoint LX (Portugal)
- ACASC (Spain)

3.3. Test used

The test selected to be introduced in the study is the OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test. A justification of the use of this test in the study, with all the details about its accuracy has been included in the annex 1.

Five thousand two hundred and fifty tests were expected to be used during the study period. They had been distributed between participating CBVCT services based on their own activity and the number of clients attended per month.

The OraQuick test was used instead off the usual test or in parallel with the usual test. Seven of the 10 participating CBVCT services (BCNCheckpoint-Hispanosida, AIDES, STOP AIDS, AIDS-Hilfe, ARAS, Checkpoint LX and ACASC) used as their usual HIV test the rapid blood test, and the other 3 CBVCT services (LEGEBITRA, Czech AIDS Help Society and National AIDS Centre) used the conventional blood test.

3.4. Study design

The study design was planned as an introductory period of 15 days of parallel testing, followed by a study period of 3 months in which both test had to be offered and the client had to choose one of them.

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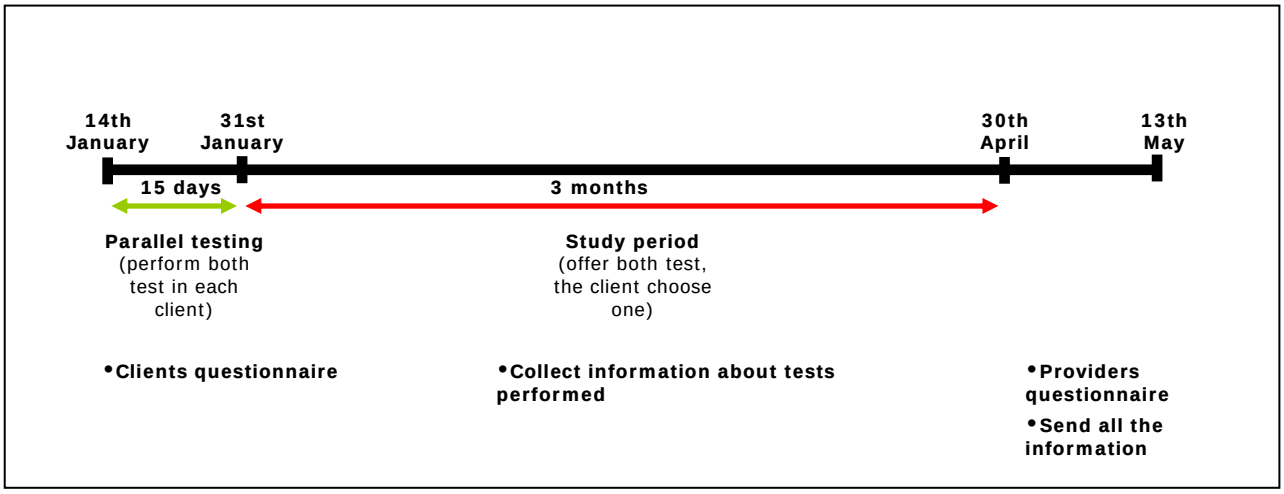
The introduction period of 15 days was to establish all necessary procedures to provide oral tests. This includes training of staff, adjustment of internal processes, and preparation of information material and/or public relations. During this initial period of 15 days, the rapid oral test had to be introduced to the CBVCT network services concurrently with the conventional test used by these services, i.e. during this period the services had to perform simultaneously rapid oral test and conventional or rapid blood test.

After this period, for a period of three months, the participating centres had to offer both oral test and the test usually used. Clients had to choose between these two possibilities.



But due to the concerns expressed by some health authorities on the use of rapid oral tests and due to problems with the ethics committees, it was decided that the centers in these situations perform parallel testing during all the study period. Some centers which are offering rapid blood HIV test and also rapid syphilis test with a blood test, thought it made no sense to ask the clients to choose, so it was decided to also allow these centers to perform parallel testing during all the study period.

Finally 6 centres performed parallel testing during all the study period, instead of let the clients choose one of both tests. The data of the centres performing the parallel testing during all the study period were useful to the assessment of feasibility, adding it to the data of the introductory period of the other centres. Some of these centres performed the clients' questionnaire during the whole study period proportioning more data for the analysis of acceptability.

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The following 6 centres performed parallel testing during the whole study period:

- BCNCheckpoint-Hispanosida (Spain)
- AIDES (France): 5 regions: Rhône-Alpes, Aquitaine, Saint-Martin, Clermont-Ferrand and Paris's region
- STOP AIDS (Denmark)
- LEGEBITRA (Slovenia)
- National AIDS Centre (Poland): CBVCT centre in Warsow and CBVCT centre in Wroclaw.
- ARAS (Romania)

The other 4 centres followed the original study design:

- AIDS-Hilfe (Germany): AIDS-Hilfe Bochum e.V., pudelwohl - gesund & schwul in DO, AIDS-Hilfe Hagen e.V.
- Checkpoint LX (Portugal)
- Czech Aids Help Society (Czech Republic)
- ACASC (Spain)

After the study period the centres had to send to the WP8 leader the following information:

- **Information related to the initial 15 days period:**
    - Number of clients tested
    - Number of reactive tests
    - Number of confirmed positives
    - Number of disagreements:
        - Rapid oral test positive, blood test negative, confirmatory test positive
        - Rapid oral test positive, blood test negative, confirmatory test negative
        - Rapid oral test negative, blood test positive, confirmatory test positive
        - Rapid oral test negative, blood test positive, confirmatory test negative
- **Information related to the 3 months study period:**
    - Number of clients tested

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        - Number of clients tested with rapid oral test
        - Number of clients tested with blood test
    - Number of reactive tests
        - Number of rapid oral reactive tests
        - Number of blood reactive tests
    - Number of confirmed positives
        - Number of confirmed positives tested with rapid oral test
        - Number of confirmed positives tested with blood test
    - Number of false positives
        - Number of false positives tested with rapid oral test
        - Number of false positives tested with blood tests
- **Information related to the same 3 month of the 2011:**
    - Number of clients tested
    - Number of reactive tests
    - Number of confirmed positives
    - Number of false positives

After the study period, a questionnaire to assess acceptability and viability of the test was distributed among all the providers.

3.5. Proposed HIV testing algorithm

In order to ensure specificity of rapid technologies, all reactive individuals with rapid oral test had to be retested using a second rapid blood test (the second rapid test was performed using the same kind of test devices with a blood sample). Independently of the result of the second rapid test, the patient was referred to health care system for confirmation, using standard procedures. The second rapid test had to be performed in order to ensure specificity of rapid technologies and to minimize the impact of a false positive result. Regardless of our study, with a positive screening test (rapid or standard) the confirmation in the health care system have to take place anyway.

The algorithm proposed is showed in the annex 2.

3.6. Questionnaires to clients and providers

A short questionnaire was administered to all the clients tested with the rapid oral test

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during the introduction period of 15 days of parallel testing (annex 3), to analyze the experience of been tested with a rapid oral test. Some of these centres performed the clients' questionnaire during the whole study period proportioning more data for the analysis of acceptability.

After the study period, a short questionnaire was distributed to all the providers (annex 4) that had been using the rapid oral test, to assess their experience and pitfalls identified.

The information of the questionnaires was summarized for each centre, in tables that were sent to each centre.

3.7. Analysis

The feasibility of introducing the oral rapid test in the CBVCT services network had been assessed by analyzing the initial 15 days period of parallel testing, and by the description of users profile and description of pitfalls identified by users during the entire period of study with the administration of questionnaires to clients and providers.

The acceptability of clients had been assessed by analyzing the clients' questionnaires and also analyzing the preferences on choosing the test in the centres which had offered both tests and had let the clients to choose one of them.

The impact of the introduction of rapid oral testing had to be analyzed by studying the variation of activity from the pre and post rapid oral test introduction: analyzing the increase in the number of tests performed and in the prevalence of positive results. This analysis was impossible due to the change in the study design. This change implies that several centres performed both tests during the whole study period, so in these centres is not possible to analyze the impact of the introduction of rapid oral testing.

4. Ethical issues

All ethical aspects of the research protocol had been considered and discussed among partners at the start-up meeting. The agreed protocol had been submitted for approval to each partner's local Ethics Committees. Approvals from all partners Ethics Committees had been gathered.

A written informed consent had been requested to all the participants (annex 6). This consent had been translated to the languages of each participating country.

This study wasn't a clinical trial. All these activities were part of a research project; clients of participating CBVCT services were not be consenting to any additional intervention because of

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participation in the project. There only was a change in the process (substitution of conventional test or rapid blood test for rapid oral fluid test).

CBVCT services don't make a diagnosis of HIV, because, in fact, most of them are not physicians, but they do a screening, and if positive the client is referred to the health system, where physicians will apply the appropriate testing algorithm for the diagnosis of HIV. Each country follows the testing algorithm marked in their national testing guidelines, which, at the same time, are based on the recommendations of UNAID-WHO-CDC testing guidelines.

The availability of ARV treatment for those diagnosed HIV positive was warranted as well the management of concomitant infections. All CBVCTs involved in the project that were already offering HIV testing had a referral system implemented. Having the commitment for the implementation of a referral system of clients with HIV reactive result was a requisite to participate in the project.

5. Results

Clients' acceptability:

In total 1,631 clients were tested with both tests (rapid oral test and rapid or conventional blood test). From those, 747 responded the questionnaire (the results are shown in table 1). The 40.8% of clients have heard about rapid oral tests before.

The 66.8% (499) were tested with rapid oral test and with rapid blood test. The rest 33.2% were tested with rapid oral test and conventional blood test.

For those tested with rapid oral test and rapid blood test, the 71.2% found the rapid oral test more comfortable but only the 47.5% preferred the oral rapid test, and the 7.7% preferred both tests equally.

For those tested with rapid oral test and conventional test, the 83.9% found the rapid oral test more comfortable but the percentage decreases to 66.1% when they are asked for their preferred test. The 78.4% didn't found the blood specimen drawing uncomfortable, the 10.4% found the rapid oral test stressful (especially the situation when reactive result of oral test needs to be confirmed and waiting (even shorter)), and the 14.4% think is better to wait a week before getting any results.

Only the 39.1% declared trusting the result of the rapid oral test, the 38.3% trust more the result of the rapid blood test and the 22.5 % reported trusting more the result of the conventional test.

The 53.2% of the clients would recommend the test to a friend, the 10,3% wouldn't

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recommend it and the 36.5% weren't sure.

Table 1. Clients's acceptability

Question	nº of answers	% of answers
Have you heard about rapid oral HIV tests before?	*n=747*	
Yes	305	40,8%
No	411	55,0%
Not sure	31	4,1%
With what kind of test have you been tested?	*n=747*	
Rapid oral test + Rapid blood test	499	66,8%
Rapid oral test + Conventional test	248	33,2%
What kind of test do you prefer?		
if you have been tested with rapid oral test + rapid blood test	*n=493*	
Rapid oral test	234	47,5%
Rapid blood test	221	44,8%
Both tests	38	7,7%
if you have been tested with rapid oral test + conventional test	*n=242*	
Rapid oral test	160	66,1%
Conventional test	82	33,9%
What kind of test have you found more comfortable?		
if you have been tested with rapid oral test + rapid blood test	*n=468*	
Rapid oral test	333	71,2%
Rapid blood test	115	24,6%
Both tests	20	4,3%
if you have been tested with rapid oral test + conventional test	*n=249*	
Rapid oral test	209	83,9%
Conventional test	40	16,1%
If you have been tested with rapid oral test + conventional test:		
Have you found the blood speciment drawing uncomfortable?	*n=268*	
Yes	46	17,2%
No	210	78,4%
Not sure	12	4,5%
Have you found the rapid oral testing stressful?	*n=278*	
Yes	29	10,4%
No	241	86,7%
Not sure	8	2,9%
Do you think that is better to wait a week before getting any results?	*n=276*	
Yes	39	14,1%
No	190	68,8%
Not sure	47	17,0%
Do you trust the result of the rapid oral test?	*n=741*	
Yes	290	39,1%
No, I trust more the result of the blood rapid test	284	38,3%
No, I trust more the result of the conventional test	167	22,5%
Would you recommend the rapid oral test to a friend?	*n=447*	
Yes	238	53,2%
No	46	10,3%
Not sure	163	36,5%

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Test selected

During the 3 months study period, in the 4 CBVCT services which followed the original study design, a total of 1188 clients could choose the oral test or the test used usually in the CBVCT (table 2 shows the results). From those, only 113 (9.5%) chose the rapid oral test. A total of 35 tests were reactive (2.95%), 3 rapid oral test (2.65%) and 32 blood tests (2.97%). 32 reactive cases were confirmed as a positives. 3 cases were false positives, 2 with rapid oral test and 1 with blood tests.

Table 2. Tests selected

3 months study period		
Clients tested	*n= 1188*	
clients testd with rapid oral test	113	9,5%
clients tested with blood test	1075	90,5%
Reactive tests	*n=35*	
rapid oral reactive tests	3	8,6%
blood reactive tests	32	91,4%
Confirmed positives	*n=32*	
confirmed positives obtained with rapid oral test	1	3,1%
confirmed positives obtained with blood test	31	96,9%
False positives	*n=3*	
false positives obtained with rapid oral test	2	66,7%
false positives obtained with blood tests	1	33,3%

Staff acceptability

A total of 67 members of staff of the CBVCT services participating answered the questionnaire after the study period (the results are shown in table3).

The 88% of the staff that have been performing the oral rapid test found the technical complexity of the test easy or very easy. The 74.3% also found the results interpretation easy or very easy. A 24.2% found the interpretation of the results not very easy, and a 1.5% found it complex.

The 6% didn't trust in the result obtained with the rapid oral test. The main reasons to don't trust completely were the longer window period compared with the blood test (rapid or conventional) using the p24 antigen; the lower accuracy of the oral test compared to blood test (rapid or conventional); the difficulty to read the result when the lines are very weak, with the possibility of give a false negative result.

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Table 3. Provider's acceptability

Question	nº of answers	% of answers
Technical complexity of the rapid oral test:	n=67	
Complex	0	0,0%
Not very easy	8	11,9%
Easy	38	56,7%
Very easy	21	31,3%
Results interpretation of the rapid oral test:	n=66	
Complex	1	1,5%
Not very easy	16	24,2%
Easy	31	47,0%
Very easy	18	27,3%
Confidence in the result obtained with the rapid oral test:	n=67	
Completelly	24	35,8%
Partially	39	58,2%
I don't trust	4	6,0%
Do you think it would be useful/helpful to have test in your service?	n=67	
Yes	38	56,7%
No	7	10,4%
I'm not sure	22	32,8%

The main advantages identified were the ease of performing the test, which it can be done at any time because it not requires venipuncture and that is not traumatic for the patients. The table 4 shows the percentages of the advantages choose by the staff. Other advantages identified were: the possibility of testing those clients with fear of needles, or not able to give blood for religious reasons, the immediacy of the result reduces the client's stress.

Table 4. Advantages identified

Question	nº of answers	% of answers
Advantages identified using the rapid oral test:	n=203 (multiresponse)	
It can be done at any time because it not requires venipuncture	38	18,7%
It is not traumatic for the patients	35	17,2%
The speed of performing the test	27	13,3%
This technology is very clean and hygienic	25	12,3%
The immediacy of the result	22	10,8%
Better acceptance of the test by clients	14	6,9%
Other	3	1,5%

Other advantages identified:

· The possibility of testing clients with fear of needles
· The possibility of testing clients not able to give blood for religious reasons
· The immediacy of the result reduces the client's stress

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The main disadvantage indicated by the staff was that the test requires a confirmatory test in case of a reactive result. The table 5 shows the percentages of the disadvantages choose by the staff. Other disadvantages identified by the staff were: the oral test has less accuracy than blood test; waiting for confirmation in the case of reactive test is very stressful; the oral test is not much useful in the centres were other blood rapid test are performed, as syphilis rapid test, because a blood sample has to be obtained anyway; the longer window period compared with the blood test (rapid or conventional) using the p24 antigen; the part of not drinking, smoking or eating 15 minutes before the test can be a major drawback; the oral test gives the idea that oral fluid could transmit the HIV infection.

Table 5. Disdvantages identified

Question	nº of answers	% of answers
Disadvantages identified using the rapid oral test:	n=69 (multiresponse)	
The test is not 100% reliable and in case of a reactive result a confirmatory test is required	46	66,7%
I some cases, the 20 minutes wait for the result is too long and the client doesn't want to wait for it	8	11,6%
The patient should be prepared in a short time for a possible positive result	7	10,1%
Other	8	11,6%

Other diasdvantages identified:

· Less accuracy than blood test
· Waiting for confirmation in the case of reactive test is stressful
· Not much useful in centres where other blood rapid tests are performed (syphilis, HCV)
· Longer window period compared with blood test (rapid or conventional) using antigen p24
· Not drinking, smoking or eating 15 minutes before the test could be a major drawback
· The oral test gives the idea that oral fluid could transmit the HIV infection

Feasibility:

In total 1,631 clients were tested with both tests (rapid oral test and rapid or conventional blood test) (the results are shown in table 6). From those, 45 obtained reactive tests (2.8%). Only 20 were confirmed since one of the CBVCT services could not gather information concerning the confirmation of their 25 reactive tests. All the reactive tests in the rest of services participating were confirmed as positives.

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Table 6. Parallel testing

Number of clients tested	1631
Number of reactive tests	45
Number of confirmed positives	20
Number of disagreements	4
Rapid oral test positive + blood test negative + confirmatory test positive	0
Rapid oral test positive + blood test negative + confirmatory test negative	0
Rapid oral test negative + blood test positive + confirmatory test positive	4
Rapid oral test negative + blood test positive + confirmatory test negative	0

There were 4 false negatives with the rapid oral test. One of them was obtained in the CBVCT AIDS FONDET, and was a case of a known HIV positive person who came to the Checkpoint because he had tested himself with a rapid oral test and was no reactive. The Checkpoint offered to test him again with rapid oral test and rapid blood test. The oral test didn't react whereas the blood test did react as expected. The other 3 false negative cases were obtained in the CBVCT from Warsaw, Poland. The CBVCT assured that the reason was the shorter window period of oral test, so in those 3 cases we shouldn't talk about false negatives, because the result was correct according the window period specified for oral test.

The staff of the different CBVCT services participating in the study identified some pitfalls or problems regarding the oral testing.

Most of them highlighted the problem of less accuracy of oral test versus blood test.

Other problem highlighted was that oral test is not much useful if multi STI screenings have to be done. If it's needed to take a blood sample for syphilis or HCV, it has more sense to use an HIV blood test rather than an oral test.

Some members of staff of centres using rapid blood test with p24 antigen or using 4th generation conventional test, declared that oral test presents disadvantages regarding its use when there is a suspicion of recent infection (since the window period for this test is longer compared with those using the p24 antigen). In fact, some counsellors recommended the blood test to the clients in cases of a suspicion of recent infection.

Other inconvenient identified by some members of the staff was that of not drinking, smoking or eating 15 minutes before the test, so it can produce some problems with the accuracy of the test.

Some providers identified as an inconvenient the complexity of the result interpretation. They

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mentioned that the direction for use was not clear and also that the pink fluid did travel up the result window very slowly and did not always disappear, making the result interpretation difficult.

In one CBVCT service, in which parallel testing was performed during all the study period, the main inconvenient highlighted by the staff was the lack of time. The oral test was performed after the blood test; the entire process for a blood test (including pre and post test interview) takes about 30 minutes, so clients would have to spend 20 minutes more to do the oral test. CBVCT service's providers are now used to the rapidity of the blood test most used during their actions that give the result after 1 minute. In some venues, people were queuing to have their test done and it was difficult to keep one provider busy during 50 minutes to perform both tests.

In one CBVCT, one member of the staff comment that oral testing feel almost more transgressing than venipuncture, because you have to operate in the mouth and that feels very private.

An almost general comment was that in general, people trust more the blood test.

Despite the problems identified, the staff also highlighted some good things about oral tests. Most of them recognize that is a good instrument to encourage periodical testing and to attract new users to the service. However, some of them said that it's good to have it as a supplement to the rapid blood test, but not as the only test in the service. Some CBVCT services said that is a very good option for offering HIV testing in onsite settings as saunas, clubs or sex venues.

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Discussion

The most comfortable test for the clients was the oral test, but the percentage is lower when the question is the test preferred. As for the preference, clients do not only take into account the comfort but the test they trust more. Only the 39.1% of participants trusted the result of the oral rapid test, versus the 38.3% and the 22,5% trusting more the rapid blood test and the conventional test respectively.

Why the clients continue trusting more blood test than oral test? One possible explanation is the attitude of the staff perceived by the client, regarding both tests. If the staff does not trust the oral test they could be partial when recommending one test or the other. Some clients asked why they have to use a test less reliable when it is possible to conduct a blood test that is more reliable. In fact, in one of the local projects of the CBVCT participating AIDS HILFE, a voluntary counsellor didn't accepted the oral test, and wanted to protect the clients from the oral test that seems less reliable to them, deciding not to offer the oral test to the clients.

The test preferences depend clearly on the kind of blood test performed in the CBVCT service, rapid blood test or conventional test. A 66.1% of those clients tested with the conventional test preferred the rapid oral test versus the 47.5% of those clients tested with the rapid blood test. These percentages are lower than the percentages of other study performed in India[21], in which the OraQuick oral fluid-based test was preferred by 87% of the participants for first time testing and 60% of the participants for repeat testing. Those results probably means that for repeat testers, which have some experience with some kind of HIV test, is more difficult to trust in another different test, and prefer the known HIV test.

Of those clients tested with oral test and conventional test, a 10.4% found the rapid test stressful, thinking in the possibility of a reactive result and having to wait for the confirmation, and a 14.4 % think is better to wait a week before getting any result, instead of obtaining the results at the moment, avoiding the stress situation of don't know if they are infected.

The percentage of clients who chose the oral test instead the blood test during the study period is very low (9.5%). This selection could be influenced in some way by the attitude of the staff member performing the test regarding both tests. Other factor influencing the selection of the test is the fact of other STI testing, as syphilis or HCV, which have to be performed with a blood sample. Clients being also tested for syphilis and/or HCV with rapid tests, preferred rapid blood HIV test, because a blood sample has to be obtained anyway. Some members of the staff stated that the oral test will be interesting when other STI oral test will be available too. Other factor influencing the selection of the test could be the fact than in some centres

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are using the rapid blood test with the p24 antigen, that make shorter the window period, and is preferred when the risk is recent and there is a suspicion of a recent infection. Most of the centres using conventional test, which has also a window period shorter than oral test (they are using 4th generation tests, which also incorporates p24 antigen).

A high percentage of the staff of the participating CBVCT services found the technical complexity of the test (88%) and the results interpretation (74.3%) easy or very easy. However, some providers identified as an inconvenient the complexity of the result interpretation. They mentioned that the direction for use was not clear and also that the pink fluid did travel up the result window very slowly and did not always disappear, making the result interpretation difficult. In the training in the use of OraQuick performed in Barcelona, clear indications of results interpretation were given, indicating that if the pink fluid not disappears of the window result the test is invalid and must be repeated.

Some providers (6%) didn't trust the result obtained with the oral rapid test due to the lower accuracy of the oral test compared to blood test (rapid or conventional), the difficulty of read the weak lines in the window result (with the risk of give a false positive result), and also the longer window period compared to the tests with p24 antigen. According to literature, OraQuick test has been used in several scenarios in United States, including labour and delivery rooms, emergency departments, outpatient clinics, services to inpatients, prisons and occupational exposures. The test has been also used in outreach programs, community-based services and in Voluntary Counselling and Testing sites. Several studies have shown good accuracy of the test in many scenarios, demonstrating sensitivity and specificity average values of 100% and 99.8% respectively[4-11] (see annex 1). So, according to literature, the sensitivity is as high as the sensitivity of rapid blood test. The specificity could be lower than a blood test, but in our algorithm it was suggested to avoid the negative effects of a false positive performing a second rapid test (blood test) in the cases of a reactive oral rapid test.

The main advantages identified were those ones related to the easy of performing, the no requirement of venopunction or finger prick, so the lack of blood, and the immediacy of the results. Those ones using rapid blood tests comment that rapid oral test has some of the same advantages of rapid blood tests.

The main disadvantage indicated by the staff, that the test requires a confirmatory test is the same in the rapid blood test. Other disadvantages identified are again the less accuracy and the shorter window period versus the blood test and the problem of multi STI testing, using blood samples. One member of the staff indicates as a disadvantage that offering the rapid

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oral test gives to the client the idea that oral fluid could transmit the HIV. Is very important that the providers explain to the clients what is tested in oral fluid are the antibodies generates against the virus, not the virus itself.

From the 45 clients tested with both tests in parallel with a reactive result, only 20 were confirmed. This is due to the lack of confirmation of the 25 reactive clients identified in the CBVCT ARAS from Romania. In this CBVCT they don't be able to follow the clients with a reactive result for the confirmation. In the rest of the CBVCT services all the reactive results were confirmed.

There were 4 false negatives with the rapid oral test. One of them was a known HIV positive. Probably this client was on antiretroviral treatment, and this is a known factor for a possible false negative. In fact, the manufacturer says oral test shouldn't be used in HIV positives on antiretroviral treatment. This is not a major problem to use this test in CBVCT because people tested aren't known HIV positives on antiretroviral treatment. And if there is some particular situation in which the CBVCT has to test a HIV positive client, during the counselling pre-test the client has to be informed that if he is under antiretroviral treatment the oral test result could be negative. The other 3 false negatives were obtained in the CBVCT from Warsaw, Poland. In Poland the test usually performed is the conventional test, using a 4th generation Elisa, which makes shorter the window period. So, in fact, those 3 cases weren't false negatives, because the result was correct according the window period specified for oral test.

Some providers identified the problem of the shorter window period of oral test compared with the blood test using p24 antigen. This could be a disadvantage, but only in cases of a suspicion of recent infection. There is an increasing body of evidence suggesting that 4th generation rapid HIV tests have little additional benefits over 3rd generation HIV kits for routine screening in low prevalence settings[22]. In the literature, some papers indicated poor results for p24 antigen with a low sensitivity in field evaluations[22-29]. However all the studies have shown good results of sensitivity and specificity of antibody detection[22-29].

Other problems identified by some providers were problems related with the performance of the oral test. One commented that oral testing feel almost more transgressing than venipuncture, because the provider has to operate in the mouth and that feels very private. A solution is to leave the client to collect the sample by itself.

Despite the problems identified, the staff also highlighted some good things about oral tests. Most of them recognize that is a good instrument to encourage periodical testing and to attract new users to the service. However, some of them said that it's good to have it as a

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supplement to the rapid blood test, but not as the only test in the service. Some CBVCT services said that is a very good option for offering HIV testing in onsite settings as saunas, clubs or sex venues.

In conclusion, the rapid oral test had a medium acceptance among the clients and the staff. The acceptability depends a lot on the kind of CBVCT service, and the kind of blood test usually performed in the centre (rapid or conventional), with a better acceptability for the clients of centres using conventional blood test, probably due to the more clear advantages of oral rapid test compared to conventional test than compared with rapid blood test. For clients of centres already using rapid blood test, the acceptability of rapid oral test is lower, probably due to the less clear advantages of oral test respect the rapid blood test; particularly if some of them have to be tested with rapid blood syphilis test or rapid blood HCV tests, so they prefer rapid HIV blood test. For those repeat testers is probable they prefer and trust more a known test than a new one. The acceptability of the clients of the oral test could be also related to the acceptability of the providers. If the providers didn't trust the oral test, clients received negative information of the test, so they didn't trust it.

Recommendations

It's important to increase the use of rapid tests in CBVCT services. The oral test should be used as a complementary method with other rapid or classic tests. The provider and the client should choose the test according the person and the scenario.

The introduction of rapid oral test in settings using conventional testing can be a good instrument to increase the number of people tested encouraging periodical testing and attracting new users to the service.

In settings using rapid blood testing, rapid oral testing can be a supplement also to attract new users and for those cases in which for fear or religious reasons the client wouldn't be able to get a blood sample.

In addition, the rapid oral test can be, in some centres, a good instrument for outreach activities of the CBVCT services.

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ANNEX 1

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Justification for the use of OraQuick Advance Rapid HIV-1/2 Antibody Test in the HIV-COBATEST project

Rapid HIV tests can play an important role in HIV prevention activities and expand access to testing in both clinical and nonclinical settings. They can help overcome some of the barriers to early diagnosis and improve linkage to care of infected persons[1]. In the last years some rapid HIV tests have been commercialized. All of them are screening tests that require confirmation if reactive. The procedure is very easy, requires no instrumentation and results are interpreted visually and are available in few minutes.

Use of oral specimens, instead of blood specimens, offers some benefits for HIV testing outside health care settings and laboratories, in point-of-care settings: is a non-invasive method, can be performed almost anywhere, eliminate costs of training and equipment to perform a blood extraction, and reduce risks of manipulating biological materials and wastes. Oral test results are available within 20 minutes after performing the test; this is an important fact that allows tested persons to know it on the same day preventing "lost to follow up".

In 2004, OraQuick Advance received the US Food and drug Administration (FDA) approval for use with oral fluid and for detection of both HIV-1 and HIV-2[2]. In 2007 the test received the CE mark required for its commercialisation in the European Union[3]. This test can be used also with a finger prick blood specimen.

OraQuick test has been used in several scenarios in United States, including labour and delivery rooms, emergency departments, outpatient clinics, services to inpatients, prisons and occupational exposures. The test has been also used in outreach programs, community-based services and in Voluntary Counselling and Testing sites.

Several studies have shown good accuracy of the test in many scenarios, demonstrating sensitivity and specificity average values of 100% and 99.8% respectively[4-11] (see annex 1). However, in December 2005, and most recently in late 2007, unusually high rates of false-positives results with the oral fluid-based OraQuick test were reported in some U.S. cities[12,13]. The field investigation conducted did not suggest a specific cause for the cluster, and the subsequent incidence study detected no false-positive tests[6,12,13]. The specificity of the test during that period was between 98.9% and 99.5%, always above the minimum threshold of specificity recommended by FDA for rapid tests (98,0%)[12,13].

As the test becomes widely used in settings with low HIV infection prevalence, false-positive

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results may occur. For that reason, following the recommendations of the CDC[12], in order to ensure specificity of OraQuick® Rapid HIV-1/2 Antibody Test and to minimize the adverse effects of false-positive result on both patients and staff, in Work Package (WP) 8 of HIV-COBATEST project, all reactive individuals will be also tested using a second OraQuick test on finger-stick whole-blood specimen. The rapid blood test, which uses blood collected from a "finger stick," has a higher specificity. Nevertheless, all reactive results should not be considered definitive. Independently of the result of eventual second rapid test, the patient will be referred to health care system for confirmation, using standard procedures.

This strategy, repeating a rapid test on finger-stick whole blood after receiving a reactive oral fluid test result, allows counsellors to provide more accurate test-result information to patients while minimizing the number of finger-stick tests that must be performed[12].

Differently to USA where the oral test has been used for several years, the implementation of oral rapid test in Europe has been scarce, because the OraQuick wasn't commercialized in Europe until 2007.

A study conducted in genitourinary medicine (GUM) clinics in London, with an HIV prevalence of 5.73%, showed a sensitivity of 93.64% (95% CI: 98.87-99.92%) and a specificity of 99.87% (95% CI: 99.28%-100%)[8]. Three false positives were found, but were attributed to reading errors. If we don't take into account these errors, then the sensitivity increases to 100%.

Other studies analyze the acceptability of oral test in different scenarios. Studies performed in U.S. have shown rapid tests have good acceptance for patients attending Emergency Departments and patients attending community-based Voluntary Counselling and Testing sites[14-16]. Another study conducted in UK, analyzed acceptability and viability of offering oral test to Primary Health patients, concluding that was viable and could be an effective measure to increase HIV testing rates in Primary Health Care[17].

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For all these reasons:

1. The use of OraQuick Advance was planned for the WP8 of HIV-COBATEST project.

2. During the first 15 days of the implementation of OraQuick test, the services will perform to each client the oral rapid test and the test used in the service, to assure the accuracy of OraQuick test.

3. The HIV testing algorithm proposed in WP8 (see annex) followed the strategy recommended by CDC, repeating a rapid test on finger-stick whole blood after receiving a reactive oral fluid test result.

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Literature review on OraQuick's performance:

Study	Study year	Place	Study period	Population	Sample	N total	N (+)	N (-)	% (+)	Sensitivity% (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)
Foglia et al., J clin microbiol 2004	2003	Kenya	2 months	U.S. Military HIV Research Program's HIV and Malaria cohort study in Kericho	blood	486	62	424	12.76	100 (92.7-100)	99.3 (86.2-98.8)	95,4 (86.2-98.8)	100 (98.9-100)
Delaney et al., AIDS 2006	2000-2005	EEUU	120 months	Diverse settings	blood	12337	327	12010	2.65	99.7 (98.3-100)	99.9 (99.8-100)	99.9	96.45
					Oral fluid					99.1 (97.3-99.8)	99.6 (99.4-99.7)	99.97	85.71
Wesolowski et al., AIDS 2006	2004-2005	EEUU	11 months	VCT, STI clinics, correctional facilities	blood	135724	1991	133498	1.47	x	99,98 (99,7-100)	99.24 (66.67-100)	x
					Oral fluid	26066	294	25685	1.13	x	99.89 (99.4-99.9)	90 (50.00-100)	x
Pant Pai et al., Plos one 2007	2004-2005	Rural India	15 months	ITS clinics (inclusion criteria: presence of risk factors or infection symptoms)	blood	450	146	304	32.44	100 (98-100)	99.7 (98.4-99.9)	98.17	100
					Oral fluid					100 (98-100)	100 (99-100)	100	100
Zelin et al., Int J STD & AIDS, 2008		UK		Patients attending genitourinary medicine clinics	Oral fluid	820	47	773	5.73	93.6 (82.5-98.7)	99.9 (99.3-100)	97.8 (88.3-99.9)	99.61 (98.9-99.9)
Pascoe et al., AIDS Patient Care and STD 2009	2006	Rural Zimbabwe	6 months	Patients presenting for VCT in rural clinics	Oral fluid	591	174	410	29.8	100 (97.9-100)	100 (99.1-100)	100	100
White et al., JAIDS 2009	2007	EEUU (Oakland CA)	2 months	Emergency Department	blood	656	4	651	0.61	x	99.85 (99.5-100)	x	x
					Oral fluid	674	0	674		x	99.85 (99.56-100)	x	x
Pavie et al., Plos One 2010	2008-2009	France (Paris)	3 months	Adults with HIV documented and 20 volunteer seronegatives , in an "outpatient clinic" of Saint Louis hospital (comparison of 5 tests)	Blood	220	200	20	x	94.5 (90.4-96.9)	x	x	x
					Oral fluid	674	0	674		86.5 (81.0-90.5)	x	x	x

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ANNEX 2

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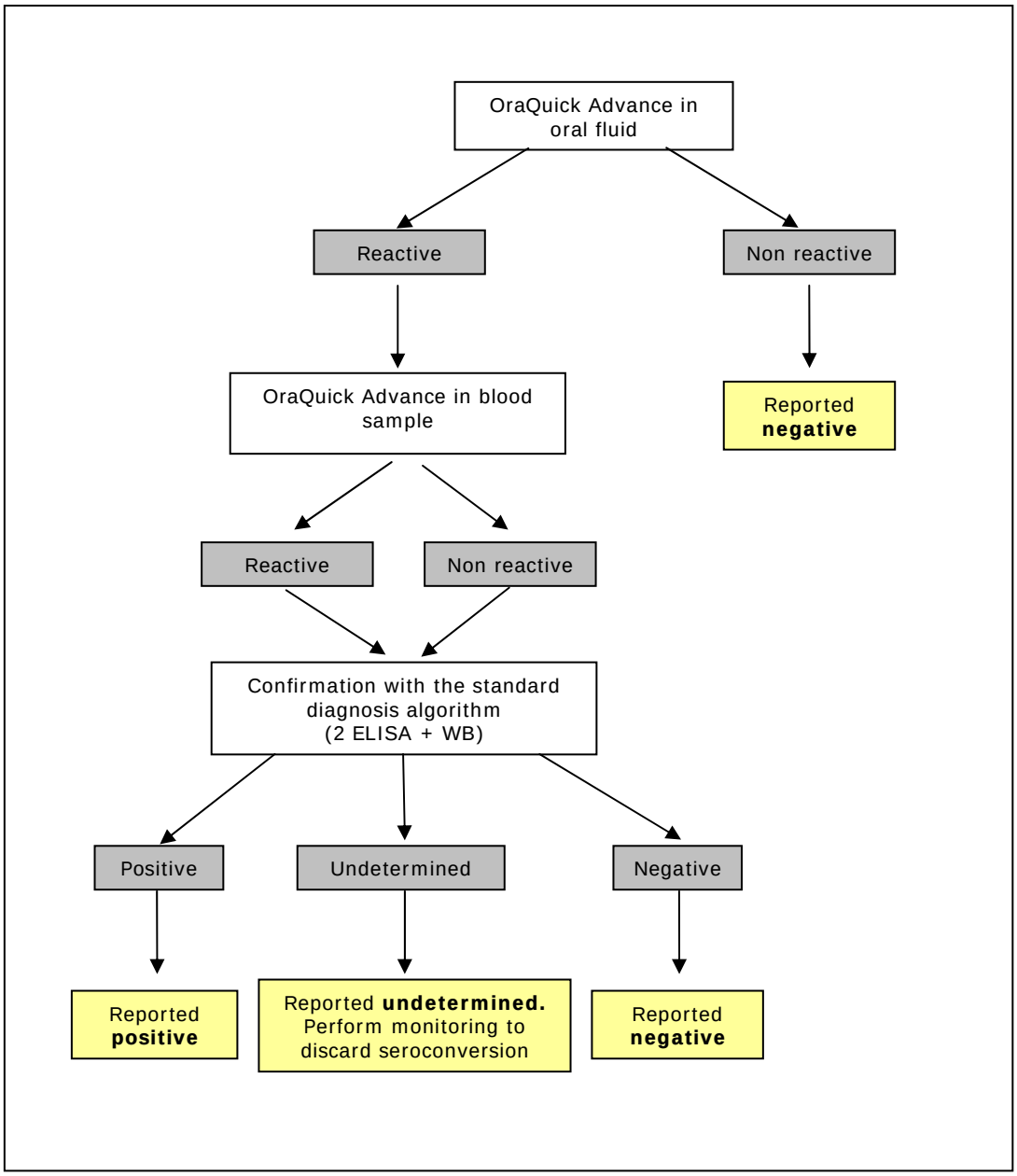
Diagnosis algorithm for HIV testing in HIV-COABATEST Project:



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ANNEX 3

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CLIENTS' QUESTIONNAIRE

(Survey used only during the first 15 days of parallel testing)

1. Have you heard about rapid oral HIV tests before?

   ☐ Yes ☐ No ☐ I'm not sure

2. With what kind of test have you been tested?

   ☐ Rapid oral test and rapid blood test

   ☐ Rapid oral test and conventional test

3. What kind of test do you prefer?

   - if you have been tested with oral rapid test and blood rapid test

     ☐ Rapid oral test ☐ Rapid blood test

   - if you have been tested with oral rapid test and conventional test

     ☐ Rapid oral test ☐ Conventional test

4. What kind of test have you found more comfortable?

   - if you have been tested with oral rapid test and blood rapid test

     ☐ Rapid oral test ☐ Rapid blood test

   - if you have been tested with oral rapid test and conventional test

     ☐ Rapid oral test ☐ Conventional test

5. If you have been tested with oral rapid test and conventional test:

   - Have you found the blood specimen drawing uncomfortable?

     ☐ Yes ☐ No ☐ I'm not sure

   - Have you found the oral rapid testing stressful?

     ☐ Yes ☐ No ☐ I'm not sure

   - Do you think that is better to wait a week before getting any results?

     ☐ Yes ☐ No ☐ I'm not sure

6. Do you trust the result of the rapid oral test?

   ☐ Yes

   ☐ No, I trust more the result of the blood rapid test

   ☐ No, I trust more the result of the conventional test

7. Would you recommend the oral rapid test to a friend?

   ☐ Yes ☐ No ☐ I'm not sure

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ANNEX 4

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PROVIDERS' QUESTIONNAIRE

(To use at the end of the study period)

1. Technical complexity of the oral rapid test:
    a. Complex
    b. Not very easy
    c. Easy
    d. Very easy

2. Results interpretation of the oral rapid test:
    a. Complex
    b. Not very easy
    c. Easy
    d. Very easy

3. Confidence in the result of the oral rapid test:
(taking into account that a reactive result always need a confirmatory test)
    a. Completely
    b. Partially
    c. I don't trust
    If you don't trust completely, why?_____

4. Advantages identified using oral rapid test:
    - The facility of performing the test
    - The speed of performing the test
    - The immediacy of the result
    - It can be done at any time because not require venipuncture.
    - This technique is very clean and hygienic.
    - It is not traumatic for the patient
    - Best acceptability by patients.
    - Other: _____

5. Disadvantages identified using oral rapid test:
    - The test is not 100% reliable and in a reactive case is needed to wait for confirmation.
    - The patient should be prepared in a short time for a possible positive result.
    - The 20 minutes waiting for the result, in some cases, is too long, and the client doesn't want to wait.
    - Other: _____

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6. Based on this experience, do you think would be convenient to dispose of this test in your service?
    a. Yes
    b. No
    c. I'm not sure

7. We are very interested in your opinions concerning rapid oral test. Please, use the space below for any comment you want to do:

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ANNEX 5

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Written Informed Consent:

Acceptability, feasibility, and impact of introducing the rapid oral test in the CBVCT network (WP8 of HIV-COBATEST Project)

The use of oral fluids instead of blood samples, offers significant advantages to performing an HIV test outside of conventional laboratory analysis: a non-invasive method, can be done almost anywhere, eliminates costs training and equipment to perform a blood extraction, and reduces the risks of manipulating biological material, as well as biological waste. Therefore, a precise oral fluid rapid test could help people with increased risk of infection to access the sample test and know their results the same day.

The aim of this study is to assess the acceptability, feasibility and impact of introducing the rapid test for the determination of antibodies against HIV-1 and HIV-2 (from OraSure Technologies OraQuick ADVANCE ®) in samples oral fluid at community-based VCT.

We would like to have your consent to participate in this study. Participation involves extracting a sample of oral fluid for the realization of rapid test for the determination of antibodies against HIV-1 and HIV-2 and the collection of some epidemiological data. The results will be completely anonymous.

In case you do not agree to the test, only a minimum of epidemiological data collected.

With this I declare that I have been informed of:

- the objectives of the study
- the methodology of the study
- the possibility to withdraw my consent to use my samples anytime
- the fact that the data will be sent to the organization responsible for analysis and processed in accordance with current legislation on data protection

Therefore, voluntarily agree to participate in the study and therefore used in biological samples that I provided.

Signature of participant: _____ Date: _____

For any clarification please contact: Jordi Casabona
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