Title: New Initiatives to develop self-testing for HIV

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Abstract

Purpose of the review: The purpose is to describe the most recent literature associated with HIV self-testing (HIVST).

Recent findings: HIVST is acceptable to a range of populations in a variety of contexts, particularly if users values and preferences are taken into account in intervention development. Approaches being explored in on-going and planned studies are the efficacy of HIVST to increase diagnosis of longstanding prevalent infections and to reduce the interval between HIV transmission and diagnosis, particularly in high incidence groups. Though there is little evidence of harms related to HIVST, this remains a potential issue. Concerns remain about the reliability of currently available HIVST kits, which have lower sensitivity than testing options available in clinical settings, particularly in early HIV infection. Evidence on linkage to care for confirmatory testing after a reactive HIVST result and the cost effectiveness of HIVST to increase rates of HIV diagnosis is currently limited.

Summary: HIVST is relatively new innovation that appears acceptable to key populations and which could increase HIV testing rates and rates of HIV diagnosis especially in at-risk groups. Concerns remain about test sensitivity, particularly in early HIV infection, and linkages to care for confirmatory testing after a reactive HIVST.
Scope of this review

The field of literature surrounding HIVST is evolving rapidly. While some key literature has been formally published, much of the most up to date and relevant evidence comes from conference abstracts. Understanding key elements of HIVST, including values and preferences in key populations most impacted by HIV is crucial. In terms of HIVST outcomes; feasibility studies, pilot HIVST projects and non-RCT intervention studies have occurred in a variety of settings, as have several randomised controlled trials (RCTs). Both RCTs and non-RCTs typically focus on interventions to detect prevalent infections, or increase testing frequency. Evidence on harm is limited, but important work is emerging. Economic evidence including cost-effectiveness analysis is very much in the nascent stages of development.

The purpose of this review is to describe the most recent literature on outcomes and issues associated with HIVST.

HIV testing rates

A high proportion of people living globally with HIV remain undiagnosed. Despite intensive interventions to increase testing over the past decade, 17.1 million of the estimated 36.9 million people living with HIV worldwide in 2014 remained undiagnosed (1). This has implications not just for individual health, with the results of the START trial in 2015 indicating antiretroviral therapy (ART) is beneficial at any CD4 count, but also for onward transmission of HIV, with 60-80% of transmission thought to occur from those as yet undiagnosed and often in the early stages of infection where risk of onward transmission is greater (2-5).

The ‘Test and Treat’ approach has been enshrined in the UNAIDS global 90-90-90 targets, which aim by 2020, to achieve 90% of people with HIV being diagnosed, 90% taking ART and 90% of those treated achieving virological suppression (6). The first ‘90’ is the largest gap with only 53% of those living with HIV currently being diagnosed. Efforts to increase testing rates has led to expansion of testing opportunities and testing interventions to meet the needs of a range of different groups in a variety of contexts (see Table 1) (7-10). HIV self-testing (HIVST) is simply the latest iteration of testing modalities.
HIV self-testing

Regulatory approval and policy

We define HIVST as when an individual takes their own sample, processes it and interprets their own result. A reactive result from an HIVST is not a diagnosis; this requires the individual to subsequently attend a testing facility for confirmatory HIV testing and linkage to care. Self-tests for a variety of other conditions are already available to the general public. HIV has long been viewed as an exceptional disease by policy makers and clinicians, and this exceptionalism meant that early in the epidemic, HIVST was banned in many countries, due to concerns over the potential for self-harm in the absence of effective treatments and the potential for coercive use (11). In recent years, the shift in HIV to a chronic manageable disease with near normal life expectancy (12, 13) through highly effective ART has led to changing attitudes towards of the impact of HIV diagnosis among clinicians and populations affected by HIV. These changes have led to a more permissive policy environment, with increasing numbers of countries enacting laws or repealing legislation making rapid diagnostic tests (RDTs) for self use available. The UK for example legalised HIVST on April 1st 2014, with the first commercially available test released the following year (Biosure™). HIVST is permitted with regulated tests available from the private sector in other countries such as the US, France, Belgium and Brazil (14). Other countries such as Australia have policies permitting HIVST, but no tests are as yet approved by the necessary regulatory agencies. Many more nations have no official policies on the technology, but unregulated HIVSTs and RDTs intended for clinical use are often available either online or through pharmacies, raising concerns about quality (14).

In efforts to continue expanding HIV testing, HIVST has been officially adopted on a global policy level, with the World Health Organisation (WHO) incorporating HIVST into their Consolidated Guidelines on HIV testing services in July of 2015 (15).

Potential benefits

HIVST has been promoted as a low cost alternative to facility based testing, potentially reducing barriers such as stigma and opportunity cost while boosting patient choice and enhancing autonomy, thereby potentially expanding testing to new groups and enabling increased testing frequency in those at highest risk (16). HIVST also has applications in intensive combination HIV prevention initiatives such as the targeted expansion of testing, treatment and pre-exposure
prophylaxis (PrEP) (16, 17). HIVSTs are available using both a whole blood sample, usually from a finger prick, or using oral fluid.

Understanding implementation contexts: values and preferences
In general studies, which seek to understand how populations might accept HIVST, tend to include participants who have not actually experienced HIVST themselves and the intervention is therefore hypothetical. Understanding this evidence remains worthwhile because it provides an indication of how populations are likely to engage with the technology, and how interventions should be delivered to ensure they are acceptable.

MSM (and to a lesser extent trans gender women and female sex workers [FSW]) in high and middle income settings are well represented in literature around HIVST acceptability as well as values and preferences, though there is little data as yet from Europe. General populations are less well represented in available data, although there is some evidence emerging from East and Southern Africa (18, 19). Recent studies report high acceptability for HIVST across a range of settings and populations. Emerging evidence from Peru (20, 21), Scotland (22), the USA (23, 24), Vietnam (25) and Mexico (26) report that MSM find HIVST highly acceptable, with moderate acceptability observed in Hong Kong (27). In a recent cross-sectional study in England, HIVST was the second most preferred location for future HIV testing and tended to have greater popularity amongst MSM less likely to test at a frequency in line with national guidelines (28).

Confidentiality, convenience, immediacy and the opportunity to increase testing frequency are commonly cited benefits of HIVST (22-25, 29-32). Barriers tend to be concerns around dislocation from care pathways, the possibility of coercive testing practices, and perceived issues with self-efficacy as well as kit accuracy (31, 33, 34).

A systematic review conducted by Figueroa, Johnson (29) provides an excellent analysis of the relative preferences of various intervention components among key populations. Evidence suggests that oral fluid RDTs are marginally preferred over finger stick or whole blood tests, although this tends to vary across country income settings and population (29). For example, a recent UK study found that MSM preferred HIVST kits using a blood sample due to concerns around accuracy with oral fluid HIVST (31). In a study in Vietnam MSM and female sex workers (FSW) preferred oral fluid HIVSTs, while injection drug users (IDU) preferred blood based kits (25). In work from the US conducted with an ethnically diverse group of high risk MSM, more frequent testers preferred blood based testing, whereas men who tested less frequently preferred oral fluid HIVSTs (35).
Demonstrating impact of HIVST: outcomes from pilot projects and RCTs

A range of feasibility studies, pilot projects and trials have provided data on the feasibility and impact of providing HIVST to different groups through an array of intervention designs. While the aims for each study vary (as does quality, particularly in feasibility and pilot studies), intervention designs tend to fall into one of two categories. The first is to detect longstanding prevalent infections among groups who have never tested or who test sub-optimally. The second is to increase frequency of testing to decrease the time between acquiring HIV infection and diagnosis, particularly in risk groups with high incidence. Evidence surrounding linkage to care in RCTs remains limited. Table two presents key RCTs planned, on-going and completed.

Detection of prevalent infections

Feasibility and pilot HIVST studies provide some evidence that HIVST will likely detect undiagnosed prevalent infections in individuals who test sub-optimally or have never tested, although it remains unclear if HIVST is more efficacious than other testing options to meet this aim. Projects in the US which focussed on reaching groups who have not previously tested or have difficulty accessing services seem to be successful in reaching MSM online (36, 37) and to an extent in sex on premise venues (38). In Vietnam, community distribution was successful in reaching MSM, FSW and IDUs in urban and rural settings (25).

Of particular interest is a cohort study conducted in Kenya which provided women with a varying number of HIVSTs to distribute to their sexual partners (39). Of 58 women recruited in antenatal care, 91% (53) distributed a kit to their partner, as did 86% (91) of 106 women in postpartum care and 75% (64) of 85 female sex workers (39). In an RCT distributing HIVSTs to pregnant women and their partners in Kenya, a significantly greater proportion of those in the HIVST arm tested for HIV compared to those randomised to SoC facility based testing. More male partners of women in the intervention group tested (90.8% vs 51.7%) and higher levels of couples testing also occurred in those in the intervention arm (75.4% vs 33.2%) (40). It is important to note that figures in both studies are based on participants’ reports of their partners’ testing behaviour and must therefore be interpreted with caution.

Reducing interval between infection and diagnosis

Efforts to increase the frequency with which at risk groups with high HIV incidence test are central to aspirations around the expansion of HIVST, and increased frequency of testing is a key benefit often
repeated in values and preferences studies conducted with key populations. Non-RCT projects which have provided participants with a number of HIVSTs with instructions to test frequently have shown that distribution in line with this intervention approach is feasible amongst trans gender women in San Francisco (32), and MSM in Brazil and Peru (21).

RCT evidence in this area is not strong, largely because studies have been underpowered to assess rates of diagnosis and therefore frequency of testing has been used as a proxy measure. In Seattle, MSM tested significantly more frequently when provided with multiple HIVSTs compared to SoC (5.3 tests compared with 3.6 over 15 months) (41). The study was too small (n=230) to show an effect on increasing HIV diagnosis (41). These findings were repeated in MSM in Australia which showed increased testing frequency among the self-testing group, which did not reduce attendance in STI clinics indicating that men in this study used HIVST largely as a supplementary option (42). Encouragingly, in both these RCTs testing frequency was increased in both frequent and infrequent testers.

Linkage to care

Linkage to care for confirmatory testing is critical following a reactive result from a HIVST. A cluster randomised trial in Malawi reported that 56.3% (524/930) of people who had a reactive HIVST subsequently linked to care for confirmatory testing (43). Similar results have been seen in other observational studies in sub Saharan Africa (39). There is as yet very limited evidence from high income settings of linkage rates after HIVST, though a planned trial as detailed below, aims to provide data in this area.

Planned studies

Two planned studies are worth noting. The HIV Self-Testing Africa Project – Research (STAR project) is a $23 million four-year study taking place in Malawi, Zambia and Zimbabwe which will be the largest investigation of HIVST to date. This project will evaluate accuracy, uptake, case finding and linkage to care through a variety of models of HIVST delivery in these three countries.

The planned SELPHI study in the UK will be the first RCT which attempts to address questions on both the ability of HIVST to detect prevalent infections and also to reduce the time between infection and diagnosis and aims to recruit 10 000 MSM in England and Wales from early 2017. The primary outcome is rates of HIV diagnosis as determined through confirmatory testing and linkage to care. This RCT will provide vital evidence for future policy makers in high-income settings and those
working with key populations on the efficacy and cost effectiveness of HIVST in increasing rates of HIV diagnosis.

**Technological issues: Sensitivity of HIVST, particularly in early HIV infection**

Reliable use of HIVST kits has been reported as highly variable in observed studies (25-99.2%) (18, 44, 45), though groups used in these studies are not necessarily reflective of those likely to need or use HIVST, which makes critical assessment of these results complex. However, sensitivity and specificity estimates for HIVST when used by self-testers are high, though would appear to be higher for whole blood based HIVST compared to oral fluid based tests (96.2-100% compared to 80-100%) (46). Promisingly, repeated exposure to and use of HIVST seems to increase the confidence and ability of individuals to perform the tests correctly (19, 23, 47).

Perhaps a more pressing concern, reflected by policy makers, commissioners and patients, is that HIVST kits have a lower sensitivity (and specificity) than those currently available in clinical settings, in particular in the period of early HIV infection known as the window period. The time from initial HIV infection to detection of infection (window period) depends on the properties of the test used. Figure 1 demonstrates the range of window periods before detection of HIV infection depending on whether antibody, antibody/antigen combination or HIV RNA tests are used. Currently available HIVST products are classed as second generation tests (antibody tests that are not laboratory run through tests), highlighting that HIVST is an innovation using older generation assays.

Manufacturers of current blood based and oral test fluid based HIVST give window periods of up to 3 months for their products. Oraquick™ also reports data indicating 95-98% detection of new HIV infection at 6 weeks and 99% by week 12 (48). Blood based antibody tests are likely to have slightly shorter window periods. In high risk populations the window period of current tests is particularly troubling, with mathematical modeling suggesting that widespread use of oral HIVST in high risk populations could potentially increase prevalence due to the long window period prior to detection of infection, and potentially a false sense of security from non-reactive HIVST results leading to greater sexual risk-taking (49).

One of the potential utilities of HIVST is for those who require frequent HIV testing such as people taking PrEP. There is concern however that using an oral based HIVST in particular may lead to an increased rate of false negative tests in early infection. During the Bangkok Tenofovir Study, staff reported non-reactive monthly oral fluid HIVST (Oraquick™) results for 8 participants (20% of all seroconversions in the study) for more than 3 months (84 days) after HIV
infection. Participants receiving Tenofovir in this study took longer to develop a reactive OraQuick™ HIVST (191.8 days) than participants receiving placebo (16.8 days) (p = 0.02) (50). This may be due to the fact that the OraQuick™ test contains only a single glycoprotein antigen (anti-gp41), so it will not identify HIV-infected individuals who fail to mount a substantial antibody response to that particular antigen, perhaps due to the presence of ART. It is likely however that HIVST kits, particularly blood based products, will improve in time with antigen detection, thus increasing sensitivity and specificity.

Potential for social harms from HIVST

When considering implementation of HIVST the potential for harm among the self-tester and the broader population are often iterated concerns. A systematic review in 2014 of a variety of self-diagnostics (including 49 papers on HIVST) found very little evidence of any harm occurring in self-testing (51). However ongoing vigilance is required for any potential negative effects as HIVST is expanded in at risk populations.

A further concern around HIVST remains is the potential for intimate partner violence (IPV) and coercive testing though there is little current evidence in this area. In a recent study involving 600 women in Kenya in which pregnant women were given HIVSTs for themselves and their partner; low and equal rates of IPV was observed in both the HIVST and SoC arms (1 incident in each) (40). However women who felt they were at risk of IPV were excluded from this study. Coercive testing has been described in Malawi, with more men than women reporting having been coerced (33, 52), but evidence suggests that this did not impact on intervention acceptability. In some cases coercion was felt to be beneficial in that it reduced personal barriers to testing indicating that ‘coercion’ conceptually must be understood in the social context within which it occurs (33).

Further avenues of exploration: economic evaluation

Evidence that HIVST will save costs to health services is currently lacking, particularly in resource rich settings though planned studies aim to fill this gap.

In sub-Saharan Africa, in a sub-study from the cluster RCT in Malawi, the mean society cost of HIVST compared with facility based testing has been estimated to be US$9.2 (95% CI: US$9.1-US$9.3) versus US$11.8 (95 % CI: US$10.8-12.9). The cost per infection detected was higher through HIVST (US$97.5) than for facilities, which ranged between US$25.2-US$76.1 (53).
Recently published evidence from Cambiano, Ford (54) assessed the potential impact and cost-effectiveness of HIVST in Zimbabwe estimating two models where HIVST was not introduced, and one where it was. They estimated that the introduction of HIVST alongside existing testing interventions would save $75 million while averting 7000 disability-adjusted life-years over 20 years. This work also found however that should linkage to cascades of care be significantly impacted, ART CD4 thresholds lowered or if HIVSTs cost significantly more than the scenario estimated cost of $3 then scenarios could emerge where HIVST was not cost effective when compared to the reference scenario.

Conclusions

Based on a review of the current of evidence HIVST is clearly acceptable and feasible to deliver to a range of populations in a variety of settings. In addition, HIVST has a role alongside other existing service provision, but it’s imperative to understand this in particular demographic, cultural and health systems contexts as well as the values and preferences of the intended end users. While HIVST seems able to encourage testing in individuals who test sub-optimally and can increase the frequency at which some individuals test, it is less clear whether it is more efficacious or cost effective at detecting prevalent infections or reducing the interval between HIV infection and diagnosis for those in high incidence groups than current testing provision. Rates of linkage to care, an essential step following a reactive result with HIVST, are unclear particularly in resource rich settings.

Improvements in kit sensitivity with shorter window periods, potentially with Ab/Ag combinations are vital to serve the needs of individuals particularly those from key populations with high incidence of infection. It is presently uncertain to what degree harms, if any, occur from HIVST and what form these harms may take. Social sciences should be key in responding to questions about harms so that these are understood from the perspective of those utilising the intervention. Economic evaluation of HIVST is in nascent stages and should be a key priority area moving forward.

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**Conflicts of interest**

The authors have no conflicts of interest.
Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

References

1. UNAIDS. AIDS by the numbers: 2015. 2015.


Legend: Nucleic acid amplification testing (NAAT) is performed to detect HIV RNA. Enzyme immunoassay (EIA) is performed to detect HIV antibody (second- and third-generation EIA) or HIV antibody/antigen (fourth-generation EIA).

Note: Figure was reproduced from ‘Diagnosis and Management of Acute HIV Infection’. This material was accessed on [16/09/2016] on the HIV Clinical Resource website (www.hivguidelines.org). The HIV Clinical Guidelines Program is a collaborative effort of the New York State Department of Health AIDS Institute and the Johns Hopkins University Division of Infectious Diseases.
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<th>Table 1: HIV testing intervention types</th>
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<td><strong>Voluntary testing and counselling:</strong> Facility-based HIV testing and counselling.</td>
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<td><strong>Community based HIV testing:</strong> Voluntary testing and counselling undertaken in a community setting such as in a van or in a commercial venue.</td>
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<td><strong>Home-based voluntary testing and counselling:</strong> Testing undertaken in a domestic setting by a trained healthcare worker.</td>
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<td><strong>HIV self-sampling:</strong> HIV testing whereby an individual takes their own sample and returns it to a lab which processes it and returns a result.</td>
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<tr>
<td><strong>HIV self-testing (HIVST):</strong> Testing where a person carries out an HIV rapid test on themselves. They take their own sample, process it and interpret their own result.</td>
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<td><strong>Supervised HIV self-testing:</strong> HIVST conducted in the presence of a healthcare worker.</td>
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<td>LSHTM, UNITAID/PSI, UCL, LSTM, CRP, WHO. HIV Self-testing Africa (STAR). Multiple studies planned.</td>
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<td>MacPherson, Corbett, Choko, Wellcome Trust. (43)</td>
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<td>Merchant et al, Rhode Island Hospital</td>
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<td>MacGowan et al. The eSTAMP Study, CDC/Emory</td>
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<td>The FORTH Study, Kirby Institute, Australia (42)</td>
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| Thirumurthy, et al. University of North Carolina, Chapel Hill (40) | | | | | | Male partner testing: 148 (51.7%) in SoC vs 90.8% of HIVST group. Difference 39.1 (ci 32.4 to 45.8)  
Couples testing: 95 (33.2%) in SoC vs 214 (75.4%) HIVST. Difference 42.1 (34.7 to 49.6).  
Disclosure 145 (50.7) in SoC vs 255 (89.8) HIVST. Difference 39.1 (32.3 to 45.9)  
1 case of IPV in each arm (women who felt at risk of IPV were excluded). |
| Stekler & Katz, University of Washington (NIH). The iTest Study (41) | | | | | | Randomized to ST (any number) or standard of care (n=230)  
Number of HIV tests during follow-up (15 mth): 5.3 ST versus 3.6.  
STI diagnosis (5% ST versus 12%).  
CL AI at 12 months (21% ST versus 22%) and 15 months (29% ST versus 24%) |
| Rodger et al, SELPHI study | | | | | | Primary outcome: diagnosis of HIV infection confirmed through linkage to UK national HIV surveillance database of all diagnosed infections. Secondary outcomes include HIV and STI testing behaviours, sexual activity and cost effectiveness of HIV ST in increasing HIV diagnosis. |