WHO / UNITAID

Landscape for HIV rapid diagnostic tests for HIV self-testing

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CONTENTS

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Abbreviations

ART	antiretroviral therapy
°C	degree Celsius
CDC	Centers for Disease Control and Prevention
CE	European Conformity
ERPD	Expert Review Panel for Diagnostics
GARPR	Global AIDS Response Progress Reporting
GHTF	Global Harmonization Task Force
GPRM	Global Price Reporting Mechanism
HIV	human immunodeficiency virus
IVD	in vitro diagnostic
NAT	nucleic acid test
PEP	post-exposure prophylaxis
PEPFAR	President's Emergency Program for AIDS Relief
PQR	Price and quality reporting
PrEP	pre-exposure prophylaxis
RDT	rapid diagnostic test
SCMS	Supply Chain Management System
STI	sexually transmitted infection
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
US$	United States dollar
USA	United States of America
WHO	World Health Organization

Executive summary

This report presents the potential for HIV self-testing to contribute to achieving global 90–90–90 targets for treatment access by 2020 *(1)*, provides projections of the demand for and supply of HIV rapid diagnostic tests (RDTs) for self-testing and summarizes the emerging market landscape for self-testing. This information will likely be useful for manufacturers, donors, national programmes, researchers and many other global health stakeholders who are exploring the potential role of HIV self-testing.

The projections and estimates rely on data from a number of sources. The projected demand for HIV RDTs for professional use are based on the World Health Organization (WHO) forecast *(2)* that is based on the number of HIV testing events reported through the Global AIDS Response Progress Reporting (GARPR) and the number of HIV RDTs procured for professional use reported through the WHO Global Price Reporting Mechanism (GPRM) and Supply Chain Management System (SCMS). The projected demand for **HIV RDTs for self-testing** is based on a model using the current forecast for professional-use RDTs and applying various scenarios derived from existing literature and research on the use of HIV self-testing.

The information on the market of HIV RDTs for professional use, as well as how many are procured and at what price base, is based on reports from the WHO Prequalification of In Vitro Diagnostics (IVDs) Programme and the UNITAID and the Price and Quality Reporting (PQR) mechanism from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). The estimated price and procurement of **HIV RDTs for self-testing** was based on manufacturer reports and were limited to products with approval from a stringent regulatory authority, defined as founding members of the Global Harmonization Task Force (GHTF).

A summary of the approval pathway for HIV RDTs for both professional use and self-testing is provided.

The main findings are as follows:

- Demand for HIV self-testing is unknown yet, based on limited knowledge about uptake and use of HIV self-testing, with an estimated minimum of 4.8 million HIV RDTs in 2018. Many possible scenarios exist, with variable uptake of self-testing by populations not currently testing for HIV, possible replacement of standard testing with self-testing (0–30%) (10–70%) and different possibilities for frequency of HIV testing by self-testing (once or twice per year), leading to very broad estimates. The potential global demand for HIV self-testing will have to be confirmed and informed by population-level estimates of the current uptake of HIV testing services.
- While many HIV RDTs that are used for professional use could be adapted for self-testing, there are some characteristics that could be challenging for users. Changes, such as reducing the number of steps, simplifying specimen collection and transfer, simplifying incubation periods and result windows, and optimizing packaging and instructions for use, among others, could improve test performance. Such modifications may not just benefit individuals who self-test, but also health workers and lay providers who often perform HIV RDTs in settings with poor visibility, inadequate

lighting and limited time and supplies. This is particularly relevant as there has been a number of reports of poor quality HIV testing and misdiagnosis in some facility and community-based settings.

- Based on reviewed reports, we identified 52 HIV RDTs available for professional use. Several commercially available tests are also approved by a stringent regulatory authority. However, only 12 are WHO prequalified and 11 are undergoing the WHO prequalification process. The majority of available HIV RDTs use fingerstick/whole blood specimens and only four RDTs use oral fluid specimens. Only one HIV RDT using oral fluid is listed as eligible for WHO procurement based on a transition criteria and none is WHO prequalified. In addition, three HIV RDTs for professional use using oral fluid are undergoing the WHO prequalification process.
- Between 2012 and 2014, a total of 243 million **HIV RDTs for professional use** were reportedly procured by the Global Fund, SCMS, the United Nations Children's Fund (UNICEF) and WHO, averaging about 81 million HIV RDTs per year. In total more than 242.2 million HIV RDTs using fingerstick/whole blood were procured, averaging about 80.7 million annually. During this same period, nearly 750 000 HIV RDTs using oral fluid were procured, averaging about 250 000 annually. The market is likely to be much larger, as these estimates reflect what is reported by donor agencies and do not include HIV RDTs procured directly from manufacturers nor HIV testing services that take place in the private and/or informal sector.
- In 2014, the cost of **HIV RDTs for professional use** ranged from US$ 0.95 to US$ 1.08, using volume-weighted average prices per smallest unit per year across the Global Fund, SCMS, UNICEF and WHO. However, the cost per HIV RDT for professional use procured in resource-limited settings by the Global Fund excluding any distributor markups and assuming ex-works, ranged from about US$ 0.50 per test to about US$ 11.00 per test. The cost of HIV RDTs using fingerstick/whole blood ranged from US$ 0.50 per test to about US$ 3.30 per test, whereas the cost of HIV RDTs using oral fluid ranged from US$ 4.00 to US$ 11.00.
- There are three **HIV RDTs for self-testing** that are formally available and approved by a stringent regulatory authority. All three countries where there is a regulated HIV RDT for self-testing are high-income settings: France; United Kingdom; United States. No RDTs for HIV self-testing are WHO prequalified. In resource-limited settings, HIV self-testing is available for research purposes only or through informal sale.
- Based on landscaping as of October 2015, 15 manufactures have been identified as interested or engaged in the HIV self-testing market. Of these, 10 are using fingerstick/whole blood-based HIV RDTs and 5 are using oral fluid-based HIV RDTs.
- The cost of regulated HIV RDTs for self-testing direct to consumers in high-income settings ranges from about US$ 31 to US$ 40 per test. The cost of HIV RDTs for self-testing in the context of research or informal sales varies considerably, as costs will vary substantially based on packaging used, volumes procured, country policies and regulations, importation taxes and fees, among other factors.

Background

Public health problem

A person's knowledge of their HIV status is essential to the success of the HIV response. HIV testing services are the gateway to treatment, prevention and care. Antiretroviral therapy (ART), voluntary medical male circumcision, prevention of mother-to-child transmission, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) all contribute to reducing HIV transmission and HIV-related morbidity and mortality *(3)*. ART is highly effective in reducing HIV-associated morbidity and mortality and can prevent onward transmission of HIV *(4–6)*. Thus, in October 2015, the World Health Organization (WHO) recommended ART be offered to all people with HIV immediately following diagnosis, regardless of clinical assessment *(7)*. The United Nations issued fast-track targets that could enable the end of the HIV/AIDS epidemic, aiming to diagnose 90% of all people with HIV, for 90% of people diagnosed with HIV to receive ART, and for 90% of those on ART to have a suppressed viral load by 2020 *(8)*. The first 90 – diagnosis of HIV – is both essential and the key challenge facing the HIV response today.

The global scale-up of HIV testing services has been significant. From 2010 to 2014, more than 600 million adults received HIV testing services in 122 low- and middle-income countries *(9)*. An estimated one half of people with HIV in Africa are now aware of their HIV status *(1)*, an increase from 2005 when only 10% of people with HIV were aware of their status *(10)*. This scale-up has been possible due to rapid diagnostic tests (RDTs), implementation of routine testing in health facilities (primarily in antenatal care and tuberculosis clinics), expansion of community-based HIV testing and task-sharing initiatives enabling trained lay providers to perform HIV testing services. With the widespread availability of ART and the widespread use of RDTs, which in a validated testing algorithm can provide same-day diagnosis, HIV testing is now routinely provided with pretest information without the requirement for pretest counselling *(3)*. For adult HIV diagnosis, WHO recommends testing strategies for high (at least 5%) and low (less than 5%) prevalence settings, as well as retesting to verify diagnosis before initiating ART *(3)*. Although HIV RDTs cannot be used to make a definitive diagnosis in children under 18 months of age, as test results are not reliable due to the persistence of maternal antibodies, RDTs can be used to assess HIV exposure and to rule out current HIV-exposed infants from 4 to 9 months of age. However, all infants and children with a nonreactive HIV RDT result should receive further testing after 18 months of age or at the end of breastfeeding as per national guidelines *(11)*. And Infants and children under 18 months who have a reactive HIV RDT should receive further testing using virological assays with a validated national testing strategy *(11)*.

Despite achievements in scaling up HIV testing, there is a substantial testing gap, as indicated above with an estimated 49% of people with HIV in Africa and 46% of all people with HIV globally, remaining undiagnosed *(1)*. Although 150 million HIV tests were performed in 129 low- and middle-income countries in 2014, a subset of 81 of these countries reported that approximately 3% of all HIV tests performed was HIV-positive. Depending on the local epidemiology and the approaches used to deliver HIV testing, the reported proportion of HIV-positive test results varies considerably *(9)*. In many settings, although there

is a growing number of HIV tests every year they are not necessarily reaching people with HIV who are unaware of their status and others who are at high risk for HIV infection.

HIV testing uptake and coverage for men continues to be lower than those for women in most countries *(3)*. Nearly 70% of adult HIV tests reported in 76 low- and middle-income countries in 2014 was among women *(9)*. Global reporting suggests this is because HIV testing is integrated successfully within reproductive health services, including antenatal care, but not consistently in other relevant clinical settings; and that male partner testing is not widely implemented or taken up *(12)*. Thus, many men remain untested and those with HIV often continue to be diagnosed late.

Key populations are also disproportionately affected by HIV and comprise approximately 40% of the 2 million new HIV infections every year *(13)*. However, testing coverage among key populations remains low and existing reports of coverage are likely overestimates due to limited data that is not representative. Low uptake of HIV testing services among key populations is not only related to availability, but also depends on acceptability and is impacted by unfriendly services, fear of stigma, discrimination and criminalization of behaviour *(13)*.

Adolescents, particularly girls, are also at a significant risk of HIV infection. In sub-Saharan Africa, adolescents are less likely than adults to be tested for HIV and it is estimated that fewer than one of every five girls (aged 15–19) are aware of their HIV status *(12,14)*. Uptake of HIV testing among adolescents is often low in settings with the highest HIV incidence and services for adolescents are sometimes of poor quality; uptake is further constrained due to laws and policies, for example, age of consent laws that prevent adolescents from accessing HIV testing services *(15)*.

These challenges require new focus and new approaches to reach people with HIV who remain undiagnosed early in their infection. Many countries and programmes are considering innovative approaches to delivering HIV testing services to achieve national and global testing targets.

Technology landscape

The potential for HIV self-testing

HIV self-testing has been proposed as an additional approach to help countries expand access to HIV testing services. WHO defines HIV self-testing as a process in which a person who wants to know his or her HIV status, collects a specimen, performs a test and interprets his or her test result, often in private *(3)*. HIV self-testing does not provide a diagnosis. All individuals with a reactive self-test result must receive further testing with a complete validated testing algorithm for diagnosis from a trained provider *(3)*. In this way, HIV self-testing represents another step in line with task sharing initiatives and efforts to increase patient autonomy, decentralize services and create demand for existing services. There are many models for implementing HIV self-testing, which vary in the level of support provided and how and where HIV self-testing kits are distributed. Approaches include support from health workers, distribution or sale in the community or a health facility, as well as sale in pharmacies, kiosks, vending machines and through the Internet *(3)*.

Credit: Dr. Fabio Caldas Mesquita, Director of the Department of IST, Aids and Viral hepatites, Ministry of Health, Brazil

HIV self-testing has been shown to be acceptable among diverse populations and in various contexts for those who may not otherwise test *(16,17)*. For those with a reactive self-test result, HIV self-testing may lead to early access to health services to establish an HIV diagnosis and linkage to prevention, treatment and care. For those with a nonreactive test result, HIV self-testing may support increased uptake of prevention interventions, such as voluntary medical male circumcision, PrEP and PEP, where the requirement for HIV testing at the time of seeking prevention services is reported as a barrier *(18–20)*. For example, in Kenya, HIV self-testing was reported to facilitate access to PEP among health workers *(19)*.

Accuracy of HIV RDTs used for self-testing can be as high as 98.9% sensitivity and 100% specificity *(21)*, particularly when there are clear and concise instructions for use that have been validated by the manufacturer for the population that is self-testing (the intended user). According to a recent review in which 14 studies where HIV RDTs were used for self-testing, sensitivity ranged from 66.7% to 98.9% and specificity ranged from 95.2% to 100% *(21)*. In this review, five studies in which the same oral fluid-based RDT was evaluated for self-testing have a pooled sensitivity of 94.3% (95% CI 90.4-96.6%) and pooled specificity of 99.5% (95% CI 98.2–99.9%) *(21)*. Some studies reporting lower sensitivity found that this was related to the use of inappropriate products, poor instructions for use requiring validation among intended users and were among self-testers with known HIV-positive status and/or using ART, as well as one study among a rural population *(21)*. In general, this performance meets and exceeds the minimum requirement of 70% sensitivity and 90% specificity proposed in the PATH target product profile *(22)*. However, WHO is currently developing standards for performance. It is important to note that no single HIV RDT can provide an

HIV-positive diagnosis; as with all HIV testing strategies, the positive predictive value will vary based on the background prevalence of the population being tested. Thus, it is critical for all reactive self-test results to receive further testing from a trained provider who can provide a definitive diagnosis.

As a discreet and convenient approach, HIV self-testing may be particularly advantageous for populations who do not routinely access health services. In a recent review of the values and preferences on HIV self-testing among key populations, acceptability was found to be high primarily because users valued its convenient and private nature *(16)*. Uptake of HIV self-testing is reportedly high among general populations in high-burden settings. In Malawi, a cluster-randomized trial had 84% population-level uptake of community-based HIV self-testing – of which 44% was first-time testers, the majority was adolescents, and 11.8% of those who self-tested was identified to be HIV-positive *(23)*. HIV self-testing may also increase uptake of HIV testing services, including the uptake of male partner testing *(24,25)*. According to a longitudinal qualitative study, HIV self-testing can enable some women to encourage their partners to test for HIV *(24)*.

HIV self-testing can also increase the frequency of HIV testing. A randomized control trial among men who have sex with men reported that those offered self-testing had a higher frequency of testing and re-testing (76%) compared to those offered standard HIV testing services alone (54%) *(26)*. Increasing the frequency of HIV testing is particularly relevant for individuals at high ongoing risk for HIV and who are advised to at least test annually. Several reports and models find that men who have sex with men would test more frequently if self-testing were available and that increased frequency would have a public health benefit, particularly where testing coverage is low *(26–30)*. In addition, HIV self-testing may ease the implementation and reduce the cost of interventions, such as PrEP, where retesting is recommended every three months *(31,32)*.

HIV self-testing may also be cost-saving and be an additional way to scale up in settings with low testing coverage and where there are health worker shortages. The potential cost-savings of self-testing has also been highlighted by a Zimbabwe-based cost-effectiveness model that states that if HIV self-testing was delivered for US$ 3, over a 20-year period Zimbabwe would save US$ 75 million and avert 7000 disability-adjusted life-years *(33)*. However, since costs are highly variable across settings further research and analysis of developing markets is needed.

Innovations and new technologies for HIV self-testing

While many HIV RDTs could be easily adapted for self-testing, there are some features that without modification could prove challenging for self-testers. According to a target product profile for HIV RDTs for self-testing *(22)*, modifications to alter the operational characteristics of existing HIV RDTs could improve performance, for example, reducing the number of steps, simplifying specimen collection and transfer, simplifying result windows and how results are interpreted, and optimizing packaging and instructions for use. These improvements not only apply to self-testing, but also could improve the quality of HIV testing services using RDTs, including when RDTs are used in community settings by lay providers. According to a review on poor quality testing and misdiagnosis of HIV status in facilities, user errors are common and reports of misdiagnosis were high at 10.5% *(35)*. Thus, it is important to remember that innovations to improve HIV RDTs for self-testing may also benefit health workers, including lay providers, who are performing HIV testing services in settings with poor visibility, inadequate lighting and limited time and supplies.

Each step for HIV testing, from the specimen collection to interpreting the final result, is critical for a correct result. At the same time, however, the more steps, the greater the risk for user error and thereby an incorrect test result. In a study in South Africa, only 3% of 265 observed HIV testing events was performed correctly, with health workers not following standard operating procedures and lacking the necessary training and equipment *(34)*. In the context of HIV self-testing, this will also most likely be challenging for those who self-test. According to a study that observed individuals self-testing for HIV, only 25% of users performed all steps correctly *(35)*. The key step identified as being prone to greatest error was collecting and transferring specimen (either fingerstick/whole blood or oral fluid) and can result in lower sensitivity

and specificity. Thus, an HIV RDT for self-testing with few steps or ideally one step could reduce the risk of a number of user errors. Opportunities to develop integrated components, such as specimen collection and transfer devices as well as integrated buffer systems, may be useful, including less painful lancets and other components that are automated to regulate the volume of specimen collected and how the specimen is transferred.

Interpretation of test results can also be challenging, particularly if lines are faint or blurred, if the incubation time is narrow, if the read time is lengthy and if the results are unstable and require a precise reading time. It is well documented that errors interpreting RDT results occur among trained users, for example, incorrect interpretation of "faint lines" and failure to read results within the stipulated time *(36,37)*. It is likely that using existing RDTs for self-testing will have similar challenges. Depending on where an individual self-tests, the environment may have poor lighting that can also reduce readability. Current RDTs that are being used for self-testing should not be read for at least 20 minutes after the sample is applied and should not be read more than 60 minutes after it is applied. This requirement may be challenging for individuals who do not have timers readily available. Settings where mobile phones or other timers and clocks are available may minimize this challenge. For even greater convenience and ease of use, a more ideal RDT for self-testing may provide a result in one to five minutes, have stable incubation times where results are stable and with result windows that are clear and easy to read, particularly to prevent faint lines that can be especially challenging to interpret. Current HIV RDTs being used for self-testing, however, do not have these characteristics and would need to be developed.

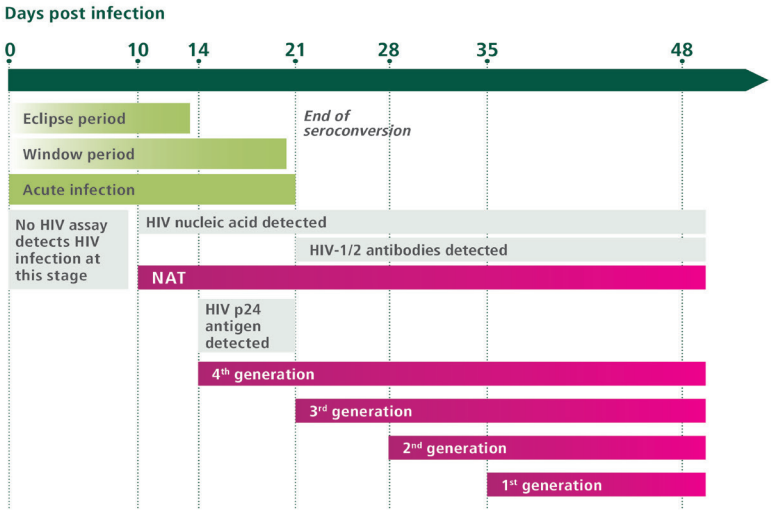
Credit: Dr. Krista Dong, ITEACH, South Africa

The product design of HIV RDTs for self-testing should also consider how the product will be transported and disposed of by users, including biohazardous materials. Even though RDTs that use oral fluid specimens pose minimal biohazardous risk, experiences and lessons learnt from blood glucose monitoring and other self-tests or self-monitoring devices should be considered as a way to minimize risk. In general, RDTs for self-testing should be designed to not only be durable, but also disposable as they will be designed for single-use yet still need to deal with a range of storage and transport conditions. This may be particularly relevant in settings with sustained high temperatures above 30 °C. However, the packaging is also a consideration for potential users who may find bulky or heavy packaging unattractive, particularly those seeking privacy and discretion.

Concerns about accuracy are a key challenge for RDTs for self-testing, as are RDTs used by trained health providers. Some studies showed that an RDT used by self-testers have a reported lower sensitivity compared to the same RDT used by trained professionals. Also, accuracy may vary depending on the RDT used for self-testing or in a professional-use setting. There are also some concerns about the risk of individuals self-testing in the "window period" – the time after infection when HIV antibodies can first be detected by a given assay (Figure 1). This is a concern for any testing approach. RDTs that are currently being used for self-testing are second generation HIV assays that reliably detect HIV infection approximately 28 days after exposure. However, in many clinical settings, third and fourth generation RDTs and molecular assays for detection of nucleic acid are used that can detect an HIV infection earlier after exposure – approximately after 21, 14 or 10 days, respectively. Therefore, one mathematical model hypothesized that if men who have sex with men substituted facility-based testing with nucleic acid test (NAT) technologies for an oral fluid-based HIV self-test, then HIV prevalence could increase *(38)*. It should be noted that this scenario is unlikely to be applicable in many low- and middle-income settings as NAT testing is not routinely provided or available. Adapting assays that are very sensitive and have a shorter window period, including third

and fourth generation RDTs and NAT technologies that can be used at the point of care, may be advantageous for populations that require frequent retesting and are at high risk for HIV. While third and fourth generation RDTs for self-testing are under development, NAT technologies for self-testing may be some years off and more costly. (The costs for NAT technologies at the point of care are estimated to be as much as US$ 20 for professional use.) Although potentially more accurate, more expensive RDTs for self-testing may be prohibitive and lead to low uptake of and access to self-testing.

Figure 1. Detecting HIV infection with various formats and generations of IVDs over the natural history of infection



Sources: WHO 2015 (3); Rosenberg 2015 (39).

There is also the potential for self-testing to improve diagnosis for other sexually transmitted diseases through multiplex testing. Combinations could include HIV, syphilis, hepatitis B and hepatitis C, among others. By introducing multiplex self-testing for HIV and other sexually transmitted infections (STIs) this could also address the potential challenge of HIV self-testing reducing the opportunity for STI screening that can be offered in facility-based testing services. This could be particularly beneficial for men who have sex with men and other key population groups. At this time, the potential for multiplex self-testing has not been fully explored and there are few multiplex RDTs for professional use. Only one HIV and syphilis RDT is WHO prequalified. There are multiplex RDTs for HIV and hepatitis B and C, but none is currently undergoing WHO prequalification. Despite the limited number of multiplex RDTs that could be adapted for self-testing, if successful, they may be a way to reach people at high risk and increase the public health impact of self-testing.

Market landscape for professional-use HIV tests

Sources of information

While there are many HIV RDTs that may be available for professional use, this report only includes HIV RDTs used to diagnose HIV-1/2 that use fingerstick/whole blood or oral fluid specimens documented in the reports listed below:[1]

- List of diagnostics eligible to tender for procurement by WHO in 2015 (including WHO prequalified diagnostics).
- WHO list of prequalified in vitro medical diagnostics.
- HIV assays: Laboratory performance and other operational characteristics, Rapid diagnostic tests (Combined detection of HIV-1/2 antibodies and discriminatory detection of HIV-1 and HIV-2 antibodies) report 18. Geneva: WHO; 2015.
- WHO Prequalification of In Vitro Diagnostics (IVDs) Programme. Annual analysis of IVDs procured by UN agencies, Global Fund and SCMS. March 2015. Unpublished.
- List of HIV Diagnostic test kits and equipments classified according to the Global Fund Quality Assurance Policy. October 2015.

Other HIV tests used at the point of care, including supplementary assays, enzyme-immunoassays (EIA) and other laboratory-based tests are not included in this report.

It is important to note that the HIV RDTs referred to in this landscape and the reports cited above primarily reflect donor-funded procurement. Countries that procure HIV RDTs directly from manufacturers are generally not represented, nor is procurement through private or informal sectors.[2]

All pricing information is based on "ex-works" prices and represents volume-weighted average prices per test and per year. Information is provided from the following procurement and funding agencies as of March 2015: Global Fund, SCMS,[3] United Nations Children's Fund (UNICEF) and WHO.

1 Because the USAID List of Approved HIV/AIDS Rapid Test Kits includes RDTs that are no longer procured, we did not use this list as a source. However, the list, as of October 2015, is available at the following link: https://www.usaid.gov/sites/default/files/documents/1864/approved-rapid-hiv-aids-test-kits-october-2015.pdf.

2 Although India and South Africa represent a large proportion of the total HIV RDT market, they are not represented in this report as they procure directly from manufacturers.

3 Data from SCMS refer to the RDTs procured through the partnership for Supply Chain Management for use in programmes supported by PEPFAR.

Approval pathway

For many countries, particularly low- and middle- income countries, evaluations and approvals by WHO, the United States Agency for International Development (USAID), the United States Centers for Disease Control and Prevention (CDC), Global Fund and stringent regulatory authorities,[4] are utilized to guide local decisions in the absence of a national mechanism or national regulation of IVDs. The procurement policies of main international funders for HIV programmes (Global Fund, President's Emergency Program for AIDS Relief [PEPFAR], UNITAID) require IVDs to be manufactured according to the applicable ISO or equivalent standards and for the IVD to be reviewed and approved or recommended by founding members of the Global Harmonization Task Force (GHTF) and/or agencies listed above. In addition, the Expert Review Panel for Diagnostics (ERPD), supported by UNITAID and the Global Fund and hosted by WHO, provides expert recommendations on the use of needed IVDs that have not yet obtained stringent approval, leading to temporary eligibility for procurement by main donor institutions.

Similar to approvals from stringent regulatory authorities, WHO prequalification of an HIV RDT for professional use involves an assessment of a product dossier that contains comprehensive information provided by the manufacturer supporting safety and performance and undertakes an onsite inspection, evaluating manufacturing and quality. The prequalification assessment relies on best international practices and is based on internationally accepted standards and guidance documents. In addition, the WHO prequalification assessment includes a performance evaluation of sensitivity and specificity, an assessment of invalid rates and an assessment of operational aspects. In general, the other approval mechanisms of non-regulatory authorities are usually comprised of an assessment of performance through a laboratory evaluation in the hands of trained users in a controlled setting.

In addition to recognizing the assessment work of international bodies, such as those noted above, some countries also have national-level product evaluation and approval requirements. Evaluation requirements may call for an HIV RDT to be assessed in the country setting or as part of a national algorithm before the IVD can be officially approved for use. Ad hoc in-country evaluations are also often used, instead of pre-market regulatory reviews, to inform product selection at the country level. Once approved for use in a country, an IVD could be procured and dispensed through the public or private sector. Lastly, within a national HIV testing policy there may also be generic regulations on how and where HIV RDTs can be used and distributed as well as who can collect specimens, perform the test, interpret the results and issue a diagnostic report.

Suppliers of HIV RDTs for professional use

Although there are many HIV RDTs available for professional use, we were able to identify 52 HIV RDTs that are listed as commercially available and/or procured as of 2012 based on reports from the WHO Prequalification of IVDs Programme; of these, 12 are currently WHO prequalified and 11 are undergoing the WHO prequalification process. Several commercially available tests are also approved by a stringent regulatory authority.

HIV RDTs are generally performed using fingerstick/whole blood-based specimens or oral fluid specimens. Out of the 52 identified HIV RDTs for professional use, 48 use fingerstick/whole blood specimens and four use oral fluid specimens.

There are 12 HIV RDTs using fingerstick/whole blood that are WHO prequalified for professional use and 8 that are undergoing the WHO prequalification process. Only one HIV RDT using oral fluid is listed as eligible for WHO procurement based on a transition criteria and none is WHO prequalified. However, three HIV RDTs using oral fluid are undergoing the WHO prequalification process.

4 Stringent regulatory authority refers to founding members of the GHTF, including the regulatory authorities from Australia, Canada, the EU, Japan, and the United States.

Pricing

In 2014, the price of HIV RDTs procured primarily by donors ranged from US$ 0.95 to US$ 1.08 per test, using volume-weighted average prices per test from the Global Fund, SCMS, UNICEF and WHO *(40)*. However, the price per HIV RDTs procured in resource-limited settings by the Global fund, excluding any distributor markups and assuming ex-works, ranged from about US$ 0.50 to US$ 11.00 per test *(41)*.

According to the Global Fund Price and Quality Reporting (PQR), prices for HIV RDTs using fingerstick/whole blood procured in resource-limited settings, excluding any distributor markups and assuming ex-works, ranged from about US$ 0.50 per test to about US$ 3.30 per test *(41)*. On the other hand, the estimated cost of HIV RDTs using oral fluid procured in resource-limited settings, excluding any distributor markups and assuming ex-works, ranged from US$ 4.00 to US$ 11.00 per test *(41)*. The prices of HIV RDT using oral fluid are based on one manufacturer; therefore, these estimates may not be generalizable to all HIV RDTs that use oral fluid.

There has been a significant decrease in price, particularly from 2012 to 2014, for oral fluid RDTs *(41)*. However, prices remain higher than RDTs that use fingerstick/whole blood.

Global demand

To meet the current demand for HIV testing services, there has been an increase in the procurement of HIV RDTs for professional use. Currently the WHO forecast suggests that from 2013 to 2018 there will be a slow growth of 6-8% annually, without factoring in increased demand for HIV testing services to achieve the first 90 target *(2)*.

According to data from the Global Fund, SCMS, UNICEF and WHO from 2012 to 2014, US$ 222.6 million was spent on procuring HIV RDTs, excluding consumables *(40)*. During this same period, 243 million HIV RDTs for professional use were reportedly procured by these agencies, averaging about 81 million HIV RDTs per year *(40)*. The real demand for HIV RDTs is likely to be much higher as these data only reflect reports from donor agencies; countries that procure HIV RDTs directly from manufacturers are not included. Additionally, some countries report a large proportion of health services and HIV testing services that occur in the private and informal sectors, for example, informal or unaffiliated community-based organizations and networks as well as alternative providers such as shamans or faith healers. Estimates of the number of HIV RDTs procured through the private sector or other informal sectors are generally unavailable. Thus, it is likely that the numbers provided in this report are underestimates and the market may be much larger.

The majority of RDTs procured in the reported period 2012–2014 were using fingerstick/whole blood: 242.2 million HIV RDTs were procured, averaging about 80.7 million annually *(40)*, while about 750 000 HIV RDTs using oral fluid were procured in same period, averaging about 250 000 annually. The use of oral fluid-based RDTs in resource-limited settings has been minimal, primarily due to high costs (the WHO/United Nations price per test is US$ 4) as well as poorer sensitivity compared to RDTs using fingerstick/whole blood and not being widely used within national testing algorithms. However, some countries that are not included in these estimates do report using oral fluid-based RDTs, particularly as a “test for triage” where individuals are tested using a single RDT and if reactive are referred for further testing and a definitive diagnosis at a health facility *(3)*.

Market landscape for self-testing use HIV tests

Approval pathway

There are, however, three HIV RDTs for self-testing that have been approved by stringent regulatory authorities for use in high-income settings. Nevertheless, no HIV RDTs for self-testing have been approved for procurement by WHO, USAID or CDC or recommended for temporary procurement by ERPD.

In resource-limited settings, HIV self-testing is primarily taking place in the context of research using HIV RDTs approved for professional use, some of which are adapted for self-testing, for example, changes in instructions for use, packaging and test components such as materials, size of components and stands for test kits. However, informal HIV self-testing is widely available through unregulated sales in pharmacies, other outlets and via Internet sites; high informal use of self-tests is reported among men who have sex with men *(42)* and health workers *(43,44)* in many settings. The outcomes of these research studies will likely inform national approval mechanisms of HIV RDTs for self-testing.

In high-income settings, however, there are examples of how HIV RDTs for self-testing were evaluated and then licensed and registered for use. In the United States, the Food and Drug Administration (FDA) premarket approval of an HIV RDT for self-testing required a three-phase clinical trial:

(1) evaluation of RDT in the hands of **trained users** in a controlled setting;
(2) (a) observed evaluation of untrained users interpreting a panel of contrived test results in a controlled setting;
(2) (b) observed evaluation of untrained users, with high, unknown and low risk of HIV, performing the RDT and interpreting the test results in a controlled setting;
(3) established performance of the test system as a whole in the hands of untrained intended and expected users in the actual intended use (in-home) setting as a measure of clinical utility *(45)*.

In addition, a performance standard was established and a risk-benefit assessment was conducted to determine the public health benefit. In France and the United Kingdom, the conformity assessment conducted for the CE marking process required the completion of both phase 2a and 2b studies in each country. A performance standard and risk–benefit assessment was not required, nor a phase 1 or phase 3 study. This was likely because the HIV RDT evaluated for self-testing was previously approved for professional use in both countries.

Within national HIV testing policies, several countries permit self-testing and outline standards for approval of RDTs, how they fit within the national HIV strategy, how RDTs for self-testing should be distributed and who can distribute or sell them. Only three countries (France, United Kingdom, and United States) have a policy allowing self-testing *and* at least one product approved for use. Some countries have a policy allowing HIV self-testing, but do not yet have a product with regulatory approval for use. Additionally, several other countries report having a policy in development and/or informal sale and use of RDTs for self-testing (Table 1).

Table 1. HIV self-testing (HIVST) policy tracking table by country as of October 2015

Policies & product(s) approved for HIVST	Policies explicitly allowing HIVST	Policies under development	HIVST available informally
USA 2012	Australia	South Africa	China
The United Kingdom 2015	Brazil	Zimbabwe	Namibia
France 2015	Kenya	Zambia	South Africa
	Hong Kong SAR; Macau SAR	Peru	Russian Federation
	Malawi	Thailand	United Republic of Tanzania
	Rwanda	Namibia	Nigeria
		Switzerland	Ukraine

Prequalification of HIV self-testing assays

The WHO Prequalification of IVDs Programme undertakes a comprehensive assessment of individual IVDs through a standardized procedure aimed at determining if the product meets WHO prequalification requirements on quality, safety and performance.

The prequalification assessment process includes three components:

- review of a product dossier;
- performance evaluation, including operational characteristics;
- manufacturing site(s) inspection.

All HIV RDTs with self-testing as the intended use submitted for WHO prequalification will undergo a prequalification assessment, as per the process described above. However, any WHO assessment that has already been undertaken for HIV RDTs intended for professional use will be leveraged according to a risk-based approach. The information required to support any claim made by the manufacturer needs to be directly linked to the intended use of the assay, in this instance, self-testing. Verification and validation data are, therefore, required in the hands of both professional users and untrained users.

Case study: Introducing HIV self-testing in South Africa opportunities and challenges

South Africa is an emerging market country with the highest number of people living with HIV in the world. The Joint United Nations Programme on HIV/AIDS (UNAIDS) defines South Africa as having a "hyper-endemic HIV epidemic" with an estimated adult HIV prevalence of 19%. The launch of the national campaign in April 2010 resulted in an increase in the number of people accessing testing. Between 2008 and 2012, annual HIV testing increased from an estimated 19.9% to 37.5% among men, and from 28.7% to 52.6% among women. Despite this increase, concern has been raised that conventional approaches are unable to close the present testing gap.

HIV self-testing is an innovation that may contribute to reaching both South African and global 90–90–90 goals. HIV self-testing has the potential to be an innovation in the South African market as it may be affordable, simple and accessible and a convenient tool to scale up testing. The market landscape for HIV self-testing in South Africa is largely undefined, but to date three self-test kits (containing two to three RDTs per package) are for sale directly to consumers for 115ZAR–199ZAR. While there are no explicit laws or policies that prohibit individuals from self-testing, it is not legal for pharmacies to sell HIV RDTs for self-testing. The Department of Health has indicated that the South African Health Products Regulatory Authority, a medical devices equivalent of the South African Medicines Control Council, has yet to be launched and its requirements for self-tests and other new products yet to be defined. Policy-makers within the Department of Health are looking forward to guidance from WHO prior to moving in the South African context. Unclear policies and regulatory barriers as well as structural and strategic barriers (e.g. limited access to distribution channels, cost of risks and uncertainty of entry, economies of scale, sunk costs, patents and technological changes) are key reasons manufacturers have been hesitant to enter the market for HIV self-testing in South Africa.

In South Africa, the Wits Reproductive Health and HIV Institute is developing large scale regulatory and programmatic assessments with several manufacturers, including Alere, Atomo Diagnostics and Orasure Technologies. These assessments will begin in early 2016 and will inform policy-making in South Africa as well as internationally.

Source: Majam 2015 (46).

Suppliers of HIV RDTs for self-testing

HIV RDTs for self-testing formally entered the market in the United States in July 2012, in the United Kingdom in April 2015 and in France in September 2015. Only three HIV RDTs have regulatory approval; one approved by the USFDA and two with CE marking: OraQuick In-Home HIV Test, Orasure Technologies LLC, Bethlehem, PA, United States; BioSure HIV Self-Test, BioSure LTD, United Kingdom; Autotest VIH, AAZ Labs, France. These HIV RDTs for self-testing are all second generation assays (Figure 1).

All three countries where there is a regulated HIV RDT for self-testing are high-income settings: France; United Kingdom; United States. No RDTs for HIV self-testing are WHO prequalified. In resource-limited settings, HIV self-testing is available for research purposes or through informal sale.

Based on landscaping, 15 manufactures have been identified as interested or engaged in the HIV self-testing market. Of these, 10 are using fingerstick/whole blood-based HIV RDTs and 5 are using oral fluid-based HIV RDTs (Tables 2 and 3). Currently, the majority of manufacturers is adapting and repackaging existing HIV RDTs for professional use for self-testing. However, there are some manufacturers seeking to develop a new HIV RDT intended for self-testing, but that could also be used for professional use.

Pricing

Prices reported for self-testing kits in high-income markets vary from US$ 31 to US$ 40 per test (Orasure Technologies' retails to consumers for US$ 40 per test; BioSure UK Ltd's HIV Self-Test retails to consumers for approximately US$ 38 per test in the United States, and in France the Autotest VIH price is approximately US$ 31 per test).

Currently, price information for HIV RDTs for self-testing is limited and largely unreported. This is because HIV self-testing has not yet been widely implemented and is occurring informally or in the context of research. The cost of HIV RDTs for self-testing for research purposes varies considerably. For instance, an oral fluid-based HIV RDT repackaged for self-testing is being procured from the manufacturer for research in different settings for US$ 3.50, US$ 11 or US$ 16 per test. However, these costs will vary substantially based on packaging used, volumes procured, country policies and regulations, importation taxes and fees, among other factors.

The cost for HIV RDTs for self-testing for informal sale also varies. Some reports do provide some estimates, however. In Namibia, HIV self-test kits currently retail direct to consumers for US$ 4–12 per test *(47)* and in South Africa HIV self-test kits are reportedly available in some pharmacies or online for approximately US$ 10 per test *(46)*.

According to the PATH target product profile for HIV RDTs for self-testing, based on consumer willingness-to-pay, at a minimum prices should be fully subsidized for poor target populations through public clinics, and country-specific commercial prices per test have been estimated as follows: South Africa: ~US$ 2–4; Kenya: ~US$ 3; Malawi: ~US$ 2.50; and non-country specific prices at ~US$ 1.06 *(22)*. While these estimates may provide a starting point, they are likely to change as self-testing is implemented more widely. Existing estimates of consumer willingness-to-pay are very limited since self-testing for HIV is largely unknown to consumers and vary widely across high- , middle- and low-income settings as well as for intended user populations.

Table 2. Pipeline of fingerstick/whole blood-based HIV RDTs for self-testing

Manufacturer assay name	Sensitivity	Specificity	Approval status	Price per test (US$)
Autotest VIH (AAZ Labs, France)	100%	99.8%	CE marked	28
Biosure HIV Self-Test (Biosure, United Kingdom)	99.7%	99.9%	CE marked	38
Exacto (Biosynex Medtech, France)	NA	NA	Submitting dossier for CE mark	NA
To be named (bioMérieux, France)	NA	NA	NA	NA
To be named JAL Innovation (Singapore) Pte Ltd	NA	NA	NA	NA
To be named (developer in Toronto, Canada)	NA	NA	NA	NA
To be named (Buchanan, USA)	NA	NA	NA	NA
To be named (Alere, USA)	NA	NA	NA	NA
atomo HIV self test (AtomoDiagnostics, Australia)	NA	NA	NA	NA
To be named (Trinity Biotech Manufacturing Ltd, Ireland)	NA	NA	NA	NA

NA, not available

Table 3. Pipeline oral fluid-based HIV RDTs for self-testing

Assay name (manufacturer)	Sensitivity	Specificity	Regulatory status	Price per test (US$)
Asante HIV Self-Test (Sedia, USA)	NA	NA	NA	NA
Aware™ 2.0 (Calypte, USA)	NA	NA	NA	NA
OraQuick In-Home HIV Test (OraSure Technologies, USA)	91.7%	98.7%	US FDA approved ; CE marked	40
OraQuick HIV Self Test (OraSure Technologies, Bangkok, Thailand)	NA	NA	NA	NA
To be named (Chembio, USA/Fiocruz, Brazil)	NA	NA	NA	NA

NA, not available

Demand for HIV self-testing

The global market demand for HIV self-testing is currently unknown and will likely vary substantially based on cost to consumers and how it is branded and distributed, as well as the local epidemiology and both the uptake of and access to existing HIV testing services.

In general, the total quantity of HIV RDTs for self-testing procured annually is unknown. In high-income settings (France, United Kingdom, United States) estimates suggest that more than 750 000 test kits have been procured. According to Orasure Technologies, from July 2012 to October 2015, the OraQuick In-Home HIV Test has sold nearly 750 000 test kits, with estimated 1–2% HIV-positive cases identified through self-testing. In addition, according to BioSure UK Ltd, since approval in April 2015, the BioSure HIV Self-Test has sold nearly 12 000 test kits, primarily in rural settings and to male users. According to AAZ Laboratories, in France, from the approval in September 2015, 70 000 test kits of Autotest VIH® have been sold to pharmacies. By the end of October 2015 more than 9 000 pharmacies in France had made the Autotest VIH® available.

Available data to estimate future demand for HIV self-testing are limited. As stated above: (i) studies have shown that some replacement of existing HIV testing services with self-testing may occur; (ii) that the frequency whereby users test for HIV using a self-test may increase; and (iii) that uptake of HIV testing by populations who are currently untested may also increase due to self-testing. However, current studies report a variety of possibilities that may not be generalizable on a global scale.

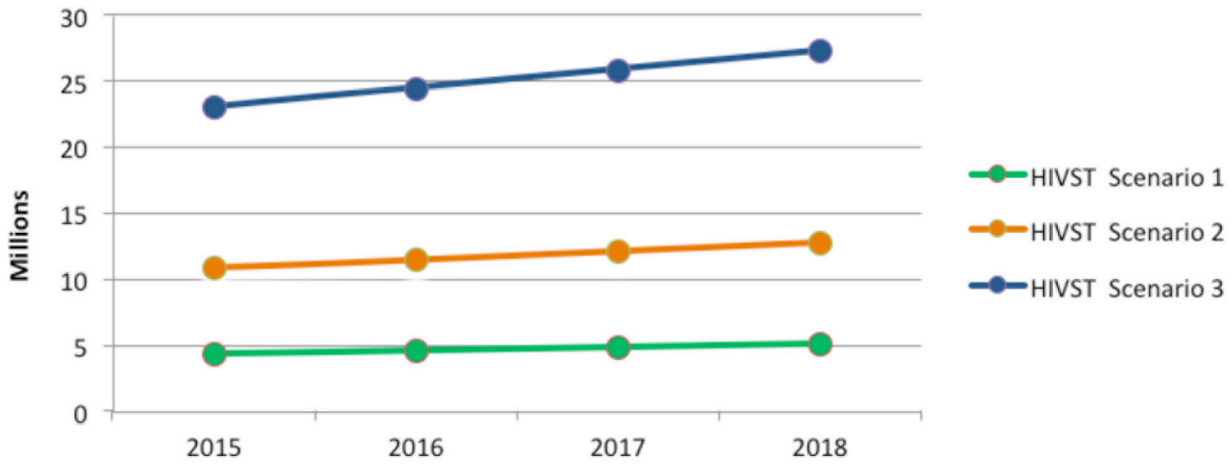
To estimate the potential demand for HIV self-testing, we created three scenarios using the forecasted number of people who would receive HIV testing services between 2015–2018 *(2)*. We assumed self-testing would be more likely to increase demand of tests not routinely offered in facilities. Therefore, we excluded 70% of reported HIV testing events which generally occur in antenatal care and tuberculosis clinic settings. We then varied each scenario by the level of substitution where users replace standard HIV testing services with self-testing; the increased frequency of HIV testing annually among users due to self-testing; and the uptake of HIV testing, using a self-test, by populations who are currently untested (Figure 3).

- **Scenario 1**: Substitution (5%), no increase in HIV testing frequency annually as a result of use of self-testing, a 10% increase in the number of people testing as a result of self-testing being available.
- **Scenario 2**: Substitution (10%), a 1.2-fold increase in HIV testing frequency annually as a result of self-testing, a 20% increase in the number of people testing as a result of self-testing being available.

- **Scenario 3**: Substitution (25%), a 1.5-fold increase in HIV testing frequency annually as a result of self-testing, a 30% increase in the number of people testing as a result of self-testing being available.

Based on these scenarios, if HIV self-testing was introduced and depending upon how substitution, frequency and uptake of HIV testing varied, demand could range between 4.3 and 23 million additional testing events in 2015, and between 5 and 27 million additional testing events in 2018 (Figure 2A). In addition to current projections of demand *(2)*, HIV self-testing could increase demand events to over 200 million HIV RDTs and testing events by 2018.

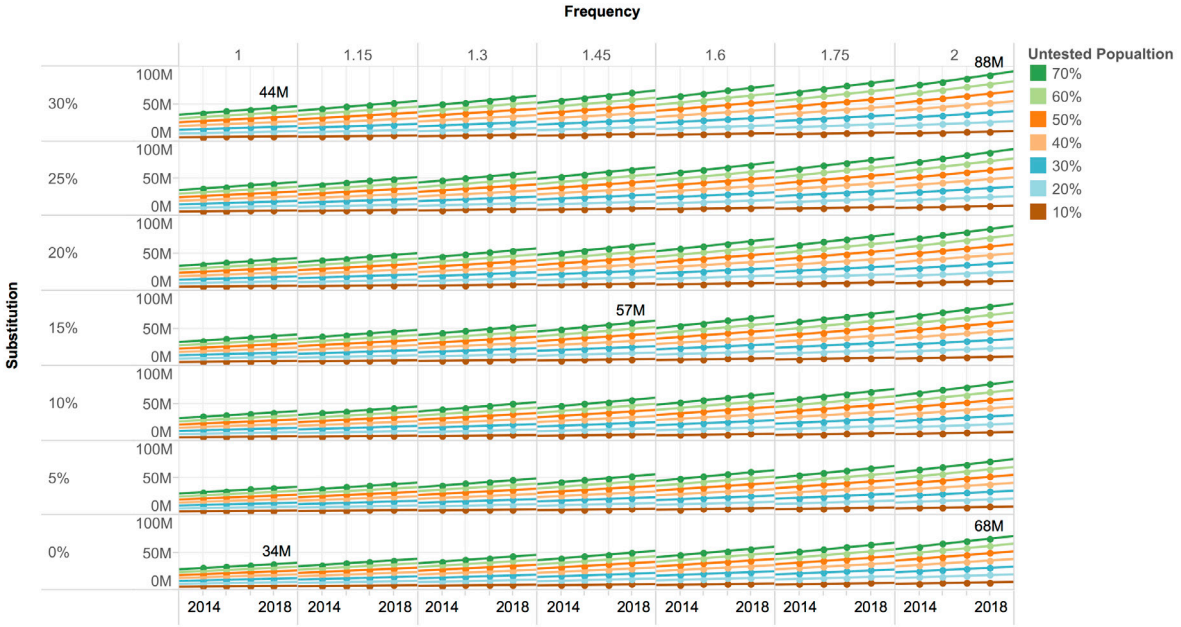
Figure 2A. Estimated demand for HIV self-testing using GARPR forecast 2015–2018



Since many other scenarios are possible, we also conducted a sensitivity analysis to reflect a number of possibilities where substitution varied from 0% to 30%, where frequency annual frequency varied from one to two times per year and the increase in the number of people testing (by 10%–70%).

Depending on the different combinations of these three variables, in 2015 demand for HIV self-testing could range from 4.1 million to 74.6 million and in 2018 from 4.8 million to 88.2 million. Based on different variables, increased frequency of HIV testing due to self-testing could have a substantial impact on potential demand estimates (Figure 2B).

Figure 2B. Sensitivity analysis of potential demand for HIV self-testing using GARPR 2015 and 2018



The potential global demand for HIV self-testing will have to be confirmed and informed by population-level estimates of the current uptake of HIV testing services. As self-testing is implemented, this will allow better-informed estimation of: (i) the level of substitution (proportion of people who replace standard HIV testing with self-testing); (ii) changes in annual frequency of HIV testing as a result of self-testing among the general population and key populations; and (iii) the extent to which the number of people testing increases due to self-testing being available (what is referred to as "untested population" in Figure 2B).

While substitution, where users replace standard HIV testing services with self-testing, may occur to some degree, it is important to note that HIV self-testing does not provide a diagnosis. Thus, HIV self-testing will ultimately have an additive role by triaging individuals who are HIV-negative to prevention services and those with a reactive self-test result to health services for further testing and, as appropriate, for treatment, prevention and care. While there may be additional and further demand for retesting following a reactive or nonreactive self-test result, the impact is speculative and such increases have not been factored into these estimates. Demand for self-testing will also vary substantially based on delivery costs for programmes and to users. The impact of pricing and willingness for programmes and consumers to pay was also not factored into these estimates.

Summary and conclusions

The demand for HIV RDTs for professional use are projected to continue to increase, without factoring in additional demand to achieve the first 90 target – diagnosis of 90% of all people with HIV by 2020. The additional approach of self-testing may also have a large impact on the demand for HIV RDTs, particularly if frequency of HIV testing increases as a result. Current estimates are limited and will need to be confirmed by population-level estimates and wider implementation of HIV self-testing; the potential of HIV self-testing is vast from a public health and a market perspective.

Opportunities for innovation not only apply to HIV RDTs for self-testing, but also may increase demand for existing HIV testing services and stimulate technological advances that may improve the quality of HIV testing by health workers and lay providers, particularly in settings where conditions are poor, training and supervision are infrequent, and resources and health worker time are limited.

Although more evidence is needed to fully understand the potential public health and market impact of HIV self-testing, this landscape provides some initial projections, estimates and a strategic summary to inform planning and thinking among diverse global health stakeholders who are exploring the potential role of HIV self-testing.

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