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Highlighting and addressing barriers to widespread adaptation of HIV self-testing in the United States

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Abstract

Introduction—HIV self-testing (HIVST), whereby an individual performs and interprets their own rapid screening test at home, is another tool to increase the proportion of at-risk individuals who know their status. Globally, HIVST has rapidly been adopted through global partnerships to ensure equitable access to tests in low- and middle-income countries (LMIC).

Area Covered—This review discusses the regulatory burdens of HIV self-testing within United States while examining the use of HIV self-tests on a global scale. While the United States only has one approved HIV self-test, numerous tests have been prequalified by the WHO.

Expert Opinion—Despite the US Food and Drug Administration (FDA) clearance of the first and only self-test in 2012, there have been no other tests that have undergone FDA consideration due to regulatory barriers. This, in turn, has stifled market competition. Despite existing evidence that such programs are an innovative approach to testing hesitant or hard-to-reach populations, high individual test cost and bulky packaging makes large-scale, mail-out, HIV self-testing programs expensive. COVID-19 pandemic has accelerated public demand for self-testing—HIV self-test programs should capitalize on this to increase the proportion of at-risk people who know their status and are linked to care to contribute to ending the HIV epidemic.

Keywords

HIV self-testing; oral self-test; blood self-test; HIV; HIVST; home-testing

1. Introduction:

Early diagnosis of HIV is essential for linkage to care, better health outcomes, and prevention of onward transmission. Among all people living with HIV in the United States, 15% are unaware of their HIV infection and account for approximately 38% of

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new infections[1 2]. Delays in diagnosis due to fear, discrimination, and stigma contributed to an estimated median time from infection to diagnosis of 39 months in 2016 [3 4].

In 1985, HIV testing first became available primarily to protect the blood supply. Subsequently, HIV counseling and testing with consent was instituted as a result of the stigma associated with HIV diagnosis, a time-consuming process for healthcare providers and a potential barrier to screening. In 2006, the US Centers for Disease Control (CDC) began recommending that all adolescents and adults be screened for HIV at least once and some populations be screened annually [5]. Even with the expansion of point-of-care (POC) tests in the past two decades, universal access to HIV testing has been difficult to achieve, with recent estimates suggesting less than 40% of the US population over 18 years of age have ever been tested for HIV [6].

2. Increasing Access to HIV Testing

Although historically dominated by reference laboratories, screening for HIV has gradually shifted to decentralized testing. Home collection for HIV tests was approved in 1996 by the US Food and Drug Administration (FDA), allowing users to collect dried blood spots (DBS) in the privacy of their own home, however, results and testing were done in centralized laboratories. Disadvantages of the tests including needing to register the tests by phone, cost of paying for a test, and a waiting period of 7 days lead to suboptimal uptake of the tests [7–9].

The FDA began approving POC HIV tests in 2002, allowing non-trained paraprofessionals to perform screening tests outside a central laboratory (CLIA-waived). [10] The rapid turnaround time allowed results to be communicated within the clinical encounter with appropriate linkage to care (either pre-exposure prophylaxis for high-risk patients who screened negative or referral for rapid antiretroviral therapy initiation for positives) concomitantly with reference lab confirmatory testing [9 11–13].

In contrast, HIV self-testing involves the collection and performance of a rapid diagnostic test on one’s oral fluid or fingerstick blood, and finally interpretation of one’s result with little or no training outside a healthcare setting (i.e., over-the-counter [OTC]). Although HIV self-testing can extend screening reach to people hesitant or resistant to testing in healthcare settings, it remains controversial due HIV stigma and potential for harm unless clearly linked to both pre-test and post-test counseling [14]. Concern for self-harm over a reactive test have existed as early as the mid-1980’s, when HIV treatments were limited [9]. Political pressure and concerns about social harm, coercive testing, point-of-sex testing, and implications of a false negative result (particularly in acute infection) are valid concerns about expanded HIV self-testing programs and need proper programmatic support to educate users [15–17].

The FDA set benchmarks of 95% sensitivity and specificity as a criterion for approval. In 2012, the FDA approved its first and only rapid oral over-the-counter HIV self-test, OraQuick® In-Home HIV Test. Although the test had excellent specificity (99.8%), it only had a 92% sensitivity in clinical evaluations. Ultimately, the FDA reviewed models that

showed with robust uptake of 2.8 million persons, an estimated 4,000 infections could be averted in the first year of use, and ultimately unanimously ruled in favor of approval for the test[18 19].

By 2015, only two other high-income countries (United Kingdom, France) had approved HIV self-tests for use [20]. Enthusiasm for HIV self-tests in low- and middle- income countries (LMICs) was evident as early as 2008, when Kenya incorporated HIV self-testing in their guidelines, despite no self-tests yet being available [21]. Without evidence for acceptability and approval by the World Health Organization (WHO), access to self-tests were limited to research and pilot studies [21]. By 2016, the WHO had enough evidence to recommend HIV self-testing as a strategy increase global access and equity [22]. Innovative implementation strategies have allowed national HIV self-testing programs to evolve in many countries, especially in LMICs [23 24].

During the COVID-19 pandemic in 2020, many public health clinics closed their doors and limited access to preventative care. Many agencies adapted their policies to offer HIV self-testing as a supplement or to replace in-person testing. Models for mail-out HIV self-test kits embedded into on-line STI self-collection public health services (e.g., I Want The Kit) had already been successfully piloted in 2013; a large randomized trial showed accurate diagnoses using self-testing kits [25]. As part of the CDC's Ending the HIV Epidemic (EHE) Initiative during pandemic times, TakeMeHome (another on-line STI testing service) offered expanded access to HIV self-tests via public health agency and community-based organization partnerships [26]. The timing was serendipitous as it coincided with the COVID-19 pandemic in-person testing service shutdown at public health clinics.

3. Regulatory Barriers to HIV Self-Testing

Since the first WHO prequalified test in 2017, there have been an additional 5 tests prequalified, either utilizing finger-stick blood or oral fluid. Two tests have been prequalified in the last year with others in the pipeline [24]. None of these companies have sought FDA clearance for their HIV self-tests (Table 1).

HIV self-tests are currently classified as Class III *in-vitro* diagnostic devices by the FDA and are subject to more stringent and costly regulations. Submission of a Premarket Approval (PMA) application costs $300,000. Additional requirements such as clinical trials, special controls and panel reviews contribute to an estimated $94 million needed to bring a Class III device to market [27 28]. Meanwhile, the majority of *in-vitro* diagnostic tests are classified as Class II devices and undergo a 510(k)-clearance process. Class II devices have a reduced regulatory burden and $13,000 application fee, with ~$31 million needed to bring a device to market [27]. WHO prequalification fees are significantly cheaper with initial fees below $20,000 and annual fees below $4000 [29].

HIV diagnostic tests were historically classified as Class III devices due to their use in screening for blood donations, however changes in testing recommendations in 2014 resulted in different test algorithms for the blood supply compared to individual testing [13]. In an attempt to improve access to HIV diagnostic devices, the FDA downgraded some POC

CLIA-waived HIV tests to Class II devices, but specifically excluded HIV self-tests from reclassification due to the requirement for specific usability controls necessary for self-tests [30]. HIV still remains an uncurable disease, stigma against people living with HIV is high, and testing for infectious diseases is inherently riskier than other diseases. However, by reclassifying certain tests, it was clear that screening for HIV was being treated as a public health good which reflected the actions and policies of community-based testing for the past decades.

The exclusion of the HIV self-testing disregards the potential impact of HIV self-tests to reach key populations resistant to engage in traditional services[3 31 32]. While the FDA acknowledges the need to improve access to HIV self-testing, they have not produced clear clinical study guidelines that would incentivize companies to apply for PMA clearance for OTC self-testing.[33] The FDA is considering alternative validation strategies for HIV self-tests, that is, for POC CLIA-waived devices to then apply for OTC clearance by providing additional userability data to be cleared for self-testing. However, FDA has not yet provided requirements or standards, leaving companies to unsure of the size of clinical trials need for approval [13].

The WHO prequalified HIV self-tests already utilize a mechanism used by FDA, requiring submission of data specific for self-testing usability. Phase II and Phase III clinical studies still need to be conducted regarding usability, and as of 2019, the FDA already accepts clinical investigations conducted outside the United States as long as Good Clinical Practices are followed [34]. The WHO has clear guidelines on the size of Observed Untrained User Studies, with smaller trials required by the WHO than FDA [18]. For example, almost 6,000 participants at 20 clinical sites were enrolled in the Phase III study (Unobserved Use Study) for the FDA 2012 PMA application, whereas the WHO requires a minimum of 900 participants and has reclassified two tests in 2022 (Observed Untrained User Study) [18 35].

Given limited resources and time, applications to the European Union and WHO are often quicker, cheaper and, potentially, more profitable than applying for PMA approval in the United States. CE (Conformité Européenne) Marking classifies HIV self-testing as its next to highest risk category (Group C), yet there are four HIV self-tests that are CE-marked (Table 1). The decentralized EU process allows for a more flexible and rapid approval of devices, resulting in a 3-year time delay for PMA-approved devices compared to CE-marked devices [36]. Importantly however, the passage of IVDR 2017/746 will likely make the CE process stricter and less flexible, which could potentially impact future approval of self-tests. In LMIC, especially in sub-Saharan Africa, collaboration between non-governmental organizations, governmental agencies and the WHO created a decentralized process to engage stakeholders to create national strategies for HIV self-testing and to remove some regulatory barriers associated with implementation of nationwide HIV self-testing programs [37].

4. HIV Self-Testing for Public Health

With its low WHO prequalification application fee, relative ease of application, and potential for large volume procurement agreements, the market has pushed the public sector price of HIV self-test kits to $1 in LMICs [38]. Initial private investment made by the Bill and Melinda Gates Foundation in 2017 brought the public sector costs for HIV self-tests to $2 per unit for 50 high-burden countries and resulted in oral HIV self-tests dominating the market for a period of time [24]. At the same time, consumer usability studies were simultaneously funded for blood-based HIV self-testing kits.

Even with low per test prices, companies are eager to apply for WHO prequalification due to ever-increasing international demand for HIV self-tests. Initiatives to increase access to HIV self-tests in Africa such as HIV Self-Testing Africa (STAR) and ATLAS procured 7.5 million tests in 2021, and are projected to have a demand of 29 million by 2025 [24]. At the same time, companies are willing to sell their product cheaply, partially due to its low cost of production. Traditional lateral flow rapid diagnostic tests, like HIV self-tests, can be produced for as low as $0.10 each depending on volume and reagent availability with usually no more $100,000 needed to develop a test [39]. Regulatory approval and adapting HIV self-tests to home use are the mostly costly aspects of device development.

The regulatory burden on companies for HIV self-tests is onerous and accounts for the high retail unit price in the US. In addition, 24-hour 7 day a week call-center to provide users contact information for local clinics HIV support services must be offered by the manufacturer as an FDA requirement has also hampered the ability for HIV self-testing programs to reach their full potential. Bulky packaging required by the FDA for HIV self-tests in the United States adds to shipping costs relative to the contents within the box—especially salient as many self-testing programs in the United States rely on mailing tests. Tests in other high-income countries have noticeably more compact packaging.

Policy decisions by the US Center for Disease Control and Prevention (CDC) in recent years have increasingly treated HIV self-tests as a public health good, similar to routine testing offered by community-based services. The CDC has funded programs to distributed approximately 100,000 kits over 8 months in 2021, all free-of-cost to users [40]. Recently, a summary of existing programs and lessons learned was published in order to provide a framework for agencies interested in expanding or initiating HIV self-testing [41]. Building on the popularity of internet-based distribution of HIV self-tests, the CDC committed $41.5 million to send 1 million self-tests over the next 5 years using internet-based orders along with further investment in community-based organizations to distribute kits [42–44].

There has been a misconception that public sector costs for HIV self-testing are significantly higher than rapid diagnostic testing performed in community-based testing [45]. In fact, the cost per self-test completed was $61 in a randomized control study targeting MSM in the United States; in comparison, a rapid test provided in an outreach setting ($113-$201) [45 46]. Although the implementation costs of a HIV self-testing program are $450,000, it ultimately becomes cost-saving due to adverted transmissions, saved lifetime HIV treatment costs, and saved QALYs [45]. Public health agencies pivoted to using HIV self-testing kits

during the COVID-19 pandemic as a risk management and triage strategy, both domestically and internationally [41].

At the same time, the private market has not been as robust as projected and hoped. Even though the Phase III trials did not meet the sensitivity threshold, the FDA chose to approve the application for the oral HIV self-test due to it's potential to result in 44,000 new diagnoses and 4,000 averted transmissions within the first year of approval [18]. These optimistic numbers were highly dependent on uptake of tests. Nearly 1 million tests were bought in the first 4 years after FDA approval, mainly through OTC pharmacy sales, though many fewer than the optimistic 2.8 million in a year modeled by the FDA [19 47]. With lackluster sales due to high cost and continued regulatory obligations, it does not seem feasible for companies to enter the US market and recoup the hefty investment needed. Willingness to pay for tests have proven to be a deterrent to uptake of HIV self-tests. A 2017 study conducted in Philadelphia showed 90% willingness to use a free HIV self-testing kit, but only 23% were willing to pay the market price of $40. [48] Other studies have studied market prices of a HIV self-test in high- income countries between $20 to $50 with varying levels of success [32 49].

5. Current State of HIV Self-Testing

The United States has a single second-generation oral fluid test, which detects only IgG antibodies.[32] Third-generation tests which detect both IgM and IgG responses have a shorter 'window period' after acute infection when serologic tests may be falsely negative as a serologic response has not yet occurred. Both the WHO and European Union have approved third generation tests (Table 1). Although, oral HIV self-tests are preferred due to their ease of collection of samples, their slightly lower sensitivity due to lower and more variable concentration of antibodies in the oral fluid may also result in a larger 'window period' of non-detection [32 50]. More research will need to be done to increase acceptability of blood-based self-tests or improve alternative detection methods using oral fluid, but the majority of tests preapproved by the WHO have been fingerstick blood.

Addressing regulatory barriers would hopefully expand access to third-generation HIV self-testing, thereby allow programs to consider further implementation strategies to ensure on-going screening within vulnerable populations and/or linkage to pre-exposure prophylaxis [25 26]. Internet-based distribution of tests has been especially effective in targeting young, first-time users and has been paired with mobile health (mHealth) interventions for access confirmation testing, mail-in STI testing, and counseling and consultations for PrEP and ART (Table 2) [7]. Community-based distribution channels (Table 2) are also utilized, but discrete distribution of self-testing kits in clinics and community engagement events is hampered by the bulky packaging required by the FDA. Continued efforts will be needed to reach not only first-time testers, but also others.

Innovative programs to link users with peer-led support for accessing follow-up care and wraparound services needs are the next step. In a modelling study done by Katz, replacing clinic based-testing with HIV self-testing would increase the prevalence of HIV, even with more frequent testing [51]. The increased prevalence of HIV was partially attributed

to a long window period, failure to link to care, and preventative services [51]. A meta-analysis on HIV self-tests saw an overall 17% reduction in linkage to care [52]. Most HIV self-testing studies show no statistical difference in positivity rates, but increased testing rates; this, in turn, increased the opportunity and need for extensive preventative services amongst those who use HIV self-tests[52–54] A meta-analysis by Figueroa found most studies pilot studies reported “intentions to link”, with the majority of users intending to seek additional testing [49]. Mechanisms to improve linkage to care and preventative services both domestically and abroad have been cited as future challenges to expanded HIV self-testing programs [37]. There is a challenging balance between the anonymity of HIV self-testing, and the need for linkage to care [37].

Offering HIV testing services in static clinics has failed to reach all priority populations at high risk for HIV transmission. Gaps still exist in use of prevention and treatment strategies in vulnerable populations, especially Black and Hispanic MSM in the United States [3]. The United States utilizes internet-based and social media distribution to target young adult populations, while also addressing geographical barriers to traditional clinic access [55].

The United States has not realized the full potential of HIV self-testing programs. Distribution models have been studied extensively in LMICs and have real translational potential to programs in the United States (Table 2). HIV self-tests have been recognized as an important component to ending the HIV epidemic internationally, and, as a result, have been integrated into existing public health programs to relative success.

6. Conclusion

Accelerated by the COVID-19 pandemic, access to HIV self-testing empowers users to know their status. However, it is clear that regulatory barriers in the US have limited the impact of HIV self-testing. Addressing these barriers can expand the number of available self-tests and, in turn, increase market competition and decrease test prices to consumers. COVID-19 has catalyzed consumer demand and understanding of self-testing. Combined with medical technologic innovation, process innovation including mail-out self-testing have accelerated access to testing and health equity. The next frontier will be to expand self-testing to include a panel of infectious organisms that can be treated to interrupt transmission (e.g., Hepatitis B, Hepatitis C, syphilis, etc.) and to develop molecular tests that are inexpensive enough to allow rapid diagnosis rather than just screening that requires confirmation [56 57].

7. Expert Opinion

Over-the-counter serologic testing for HIV has been controversial due to imperfect sensitivity particularly in acute infection (i.e., window period), and a lack of general knowledge regarding self-testing. The COVID-19 pandemic has accelerated the general public’s understanding of self-testing as well as point-of-care testing. Expanded access to OTC tests has proven to be a public health tool for knowing one’s status and epidemic control, as evidenced by widespread distribution of free OTC SARS-CoV-2 rapid antigen tests. Access to self-testing during epidemics is good for both individuals and public health.

Global access to HIV self-tests has been a model that is instructive for the US. Not only are HIV self-tests cheaper to distribute, they are also widely accepted by governments, non-governmental agencies and users. The continued global purchase of HIV self-tests will hopefully fuel innovation for rapid fourth generation test (to detect acute infection), inexpensive molecular self-tests, or novel integrated distribution models. The US could learn distribution innovation from LMIC to improve access to self-testing. An important barrier has been FDA clearance which is expensive. At present, WHO pre-qualification is much less costly than FDA clearance; only one test has been approved in 2012. These issues could continue to hamper innovation and accessible testing for years to come.

The procurement of HIV self-tests increased rapidly from 1 million tests bought in 2017 to a 29 million projected by 2025 [24]. If interest in self-tests tests is sustained, there will lead to a projected $104 million shortfall by 2025 [24]. While knowing ones' status is empowering, HIV self-testing program detractors will demand more quantitative data regarding linkage to care and access to preventative services to justify continued investments in HIV self-testing programs.

While HIV self-testing programs have expanded since being first introduced in Malawi, Zambia, and Zimbabwe in 2015 as part of STAR's Phase I implementation, further phases expanded into middle-income countries such as South Africa and India. Recent US investments in OTC devices during the COVID-pandemic shows the universal appeal of self-testing. The serendipitous expansion of HIV self-testing in the United States during COVID-19 shows that HIV self-testing has a place in high-income countries. More self-test options can accelerate HIV-self-testing to accelerate the end of the HIV epidemic.

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Article Highlights:

- HIV self-testing access has expanded globally, particularly in low- and middle-income countries.
- Regulatory barriers have dissuaded companies from applying for FDA approval for their HIV self-tests.
- HIV self-tests are an effective tool to reach hesitant-to-test populations.
- Distribution models in LMICs have shown the potential for HIV self-testing programs in the United States.
- HIV self-testing is an important component of ending the HIV epidemic which could be accelerated by regulatory reform.

Table 1:

HIV Self-Tests on Market

Test (Manufacturer)	Specimen	Antibody	Approval	Price per test
OraQuick® In-Home HIV Test (OraSure Technologies, USA)	Oral	2nd generation, HIV ½ antibodies	FDA	Retail Market USA: $40[24] Public sector: $7.50–$26[5758]
OraQuick® HIV Self-Test (OraSure Technologies, USA)	Oral	2nd generation, HIV ½ antibodies	WHO PQ, CE Mark	Public sector LMIC: $2[24]
INSTI® HIV Self Test (bioLytical Laboratories Inc., Canada)	Blood	2nd generation, HIV ½ antibodies	WHO PQ, CE Mark	Retail HIC: $25–40 LIC public: $3–6 LIC retail: $6–14
SURE CHECK® HIV Self-Test (Chembio Diagnostic Systems, Inc, USA)	Blood	2nd generation, HIV ½ antibodies	WHO PQ, CE Mark	Based on volume of testing: LMIC: $2.99
Mylan HIV Self-Test (Atomo Diagnostics Pvty. Ltd, Australia)	Blood	3rd generation, HIV ½ antibodies	WHO PQ, CE Mark	Public sector: $1.99 for 135 countries
Check Now® HIV Self Test (Abbott Rapid Diagnostics, Germany)	Blood	3rd generation, HIV ½ antibodies	WHO PQ	LMIC: $1.50
Wondfo HIV Self-Test (Guangzhou Wondfo Biotech Co., Republic of China)	Blood	3rd generation, HIV ½ antibodies	WHO PQ	Public Sector LMIC: $1[38]

* Adapted from Unitaid and WHO report in vitro diagnostics [57]

FDA = Food and Drug Administration; WHO = World Health Organization; PQ = prequalified HIC = High-income countries; LIC = Low-income countries; LMIC = Low- and middle- income countries; Retail= bought on by customers (pharmacy, over-the-counter); Public-sector = per unit cost sold by procurement agreements (non-governmental agencies, public health agencies or ministries)

Table 2:

Distribution Model Opportunities in the United States

Model	Target Population	Distribution Model Description	Countries/Program Implemented	Potential opportunities in United States
Online Ordering	MSM (usually)	Ordering on internet and sent via mail.	Thailand[59], China [60], Australia[61], Hong Kong [62]	United States[26]
Social Media/ Mobile Apps	Young adults with access to mobile devices and the internet MSM on dating sites	Users can use mobile apps to allow for referrals and help when needed	South Africa[63], China [64], Kenya [64], United Kingdom[64]	Dating Apps (Grindr) [65] Mobile Apps [6667]
HIVST Fixed Sites	High risk adults and adolescents	Outpatient settings, pharmacies, HTS clinics, STI consultations.	STAR[68], ATLAS [69]	Let's Stop HIV Together[41], Emergency Department [70–73]
Integration into mobile clinics	High risk men who are afraid of HIV test results	HIVST are offered in mobile voluntary male circumcision mobile clinics	STAR[2064]	Mobile Health Clinics
Door-to-Door	Rural populations, those unable/unwilling to access care	Community-based distributors offer HIVST and help if requested	Zambia[74], Malawi[75] Zimbabwe [76]	Oregon study[55],
Peer Distribution	Sexual partners of newly diagnosed HIV+ person. Partners of pregnant women. High risk population of FSW. Male dominated industries (mining, trucking, farming)	Index newly diagnosed HIV+ to social network Pregnant patients receive HIVST for their sexual partner during antenatal care. Distribution via female sex workers to at-risk peers Peer Distribution via coworkers	Malawi [77] Malawi [77] STAR [68], ATLAS [69] Uganda [78–80], South Africa [81]	MSM Peer Distribution [8283]
Hot Spot Distribution	High risk adults, adolescents (young women and girls)	Distribution in high traffic areas (taxi stands, bus or truck stops, shopping centers)	Kenya [84], South Africa [85]	Vending machines in Los Angeles[58], Bathhouses[86]