Target Product Profile: HIV Self-Test Version 4.1

White paper on the evaluation of current HIV rapid tests and development of core specifications for next-generation HIV tests

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About PATH
PATH is an international organization that drives transformative innovation to save lives and improve health, especially among women and children. We accelerate innovation across five platforms—vaccines, drugs, diagnostics, devices, and system and service innovations—that harness our entrepreneurial insight, scientific and public health expertise, and passion for health equity. By mobilizing partners around the world, we take innovation to scale, working alongside countries primarily in Africa and Asia to tackle their greatest health needs. Together, we deliver measurable results that disrupt the cycle of poor health. Learn more at www.path.org.

Contents

1.0 Introduction to the target product profile

This annotated target product profile (TPP) describes the desired characteristics of an HIV self-test. To identify the requirements presented in the TPP, PATH staff collected data from the scientific literature, interviews, user-based studies, and laboratory evaluations of HIV rapid tests and HIV self-test prototypes. Because not all data agree, the PATH team placed values on data to prioritize use. Where possible and constructive to the discussion, this document discusses differences in the data.

The minimum requirements identified in this TPP are the performance and use characteristics needed for a minimally acceptable level of performance as identified by stakeholders. The optimistic requirements are the performance and use characteristics of an ideal product.

This TPP is intended to be forward looking—targeting a desired product profile at the time of launch. The rapidly evolving field of HIV self-testing lends itself to short-, medium-, and long-term objectives that can be met with different products that embrace the TPP in varying degrees. This TPP, as with any TPP, is a living document that is meant to be updated as new evidence accumulates and the field evolves. In its current iteration, the TPP includes evidence from stakeholders and early usability studies in Kenya, Malawi, and South Africa.

The purpose of the TPP is to provide a common foundation for the development of HIV self-tests that contains sufficient detail to allow device developers and key stakeholders to understand the characteristics a test must have to be successful. The TPP also contains information on additional features that would make a test more attractive. Ultimately, trade-offs in features may need to be made, and the supporting information can help to prioritize attributes.

This document consists of an executive summary and annotations. The executive summary is a high-level overview of core TPP variables and may be especially useful for discussions and presentations. The annotations provide a detailed guide through the TPP, capturing details, examples, and the rationale supporting the minimum and optimistic targets for each requirement and variable. Where appropriate, questions related to the variables are raised and addressed. If important contradicting opinions or data related to a variable exist, these are raised and, where possible, explained.

In summary, this TPP lays out a clearly defined lowest level of acceptable performance and use characteristics for an HIV self-test. Careful formulation of these criteria provides a baseline for developing new tests well suited for implementation.

2.0   Executive summary

2.1   Overview

Although the concept of HIV self-testing was first considered more than 20 years ago, only recently has HIV self-testing gathered popular support. Use of rapid HIV tests for self-testing was reported as early as 2007 by health workers in Kenya. The first test specifically marketed for HIV self-testing was approved by the US Food and Drug Administration (FDA) in 2012. The tools available for HIV self-testing are rapid tests originally developed for provider-based testing that have been repackaged. HIV self-testing is a different use case scenario from provider-based testing and merits consideration of tools with features that are appropriate for the nuances specific to self-testing.

Reported barriers to routine, provider-based HIV testing include lack of confidentiality and privacy,[1] fear of testing and stigma, and timing of testing and waiting time to do the test.[2,3] It is plausible that a well-designed HIV self-test could successfully break down these barriers and make HIV testing more attractive, especially to populations not currently seeking any form of HIV testing.

This TPP is a result of thoughtful review of currently available literature, interviews with key informants/stakeholders, laboratory-generated data on the performance of rapid tests, and usability assessments of test features with naïve users in sub-Saharan Africa. Many similarities exist between the desired characteristics of HIV self-tests and provider-based HIV tests. In fact, it is reasonable to believe that the short-term market need for HIV self-tests can be addressed through the current strategy of re-packaging and labeling currently existing HIV rapid tests.

We have noted that features currently available in rapid tests are not ideally suited for self-testing. Areas where improvements will have the greatest impact are sample collection and transfer to the test device, test complexity (including the number of steps required), packaging, instructions, and interpretation of results.

2.2 Target product profile: Summary table

Requirement category	Variable	Minimum requirements	Optimistic requirements
Context (use case)	*Proposed use and value proposition*	Rapid diagnostic test (RDT) to detect chronic HIV infection in target users.	RDT to detect early-stage and chronic HIV infection in target users.
	Target population	Persons seeking to learn HIV status through non-clinic/provider/assisted based testing.	Persons seeking to learn HIV status through non-clinic/provider/assisted based testing.
	Target countries	Countries that bear the burden of the HIV epidemic and have the highest rates of unmet testing. Countries that have the health infrastructure to launch HIV self-testing.	All countries.
	Infrastructure level	Minimal infrastructure sufficient for self-testing in a private setting; no cold chain support; no electricity or clean water requirements.	Minimal infrastructure sufficient for self-testing in a private setting; no cold chain support; no electricity or clean water requirements.
	Special populations	Populations to include low socioeconomic status and women of childbearing-age and specific target groups (discussed in target population above).	Populations to include low socioeconomic status and women of childbearing-age and specific target groups (discussed in target population above).
	Fit with Clinical Workflow/Linkage to Action (Care)	Instructions on next steps and for seeking care based on the test result.	Minimum plus access in-person or live phone-based, SMS or other on-demand mechanism for counseling and referral.
	Data handling	Developed communication system that will instruct target users on linking and reporting HIV self-test results with appropriate care (follow-up testing and counseling).	Developed communication system that will instruct target users on linking and reporting HIV self-test results with appropriate care (follow-up testing and counseling. Additional work may be required to define additional optimal requirements.
	Analyte	Qualitative detection of HIV infection, antibody.	Qualitative detection of HIV infection, antibody, biomarker, and nucleic acid.

Requirement category	Variable	Minimum requirements	Optimistic requirements
Context (use case)	*Platform/methodology*	Immunochromatography, and immunofiltration.	Immunochromatography, immunofiltration, microfluidic, and others.
Performance requirements	*Precision/concordance*	Concordance >99%	Concordance >99%
	Clinical sensitivity and specificity	Sensitivity >99% Specificity >98%	Sensitivity >99% Specificity >99%
	Analytical sensitivity and specificity	Sensitivity >97% Specificity >97%	Sensitivity >99% Specificity >99%
	Reference method	Days before Western Blot (WB) positive: 0 Days since Nucleic Acid Test (NAT) reactive: 24	Days before WB positive: 25 Days since NAT reactive: 0
	Field performance	Sensitivity >70% Specificity >90%	Sensitivity >90% Specificity >98%
	Rate of errors in device interpretation	Correct interpretation rates: 98% for negative, strong positive, and invalid; 95% for low positive.	No interpretation needed.
	Device failure/invalid rate	<5%	<1%
	User-induced failure rate	<20%	<10%
	Interferences	Low risk of interferences.	No interfering factors.
User requirements	*Instructions for use*	Pictorial instructions clearly detailing all test components and steps.	Pictorial instructions with text targeted to a fifth-grade reading level; text available in English and local language(s). All test components and steps need to be clearly detailed.

Requirement category	Variable	Minimum requirements	Optimistic requirements
User requirements	*Result interpretation*	Clear positive, negative, or invalid result with minimal instructions for interpretation. Instructions for interpretation clearly match actual. User can interpret weak positives correctly 95% of the time.	Results can be interpreted correctly 95% of the time without instructions.
	Result presentation	The result can be read with the naked eye or with an integrated reader. Result wells should be clearly marked and/or not require much instruction or explanation to interpret. Test and control lines are easily distinguishable.	Results are presented in a manner that is self-explanatory and need little or no instructions or explanation to interpret. No weak color lines (and only strong results).
	Level of complexity	Low number of test steps (e.g., three to five) that are easy to conduct.	One easy and intuitive operator step (not timed), excluding waste disposal.
	Training required	User able to conduct test correctly after brief review of instructions. Support available in case of questions.	Conducting test is self-explanatory and intuitive. No training needed. Support available in case of questions.
Operational requirements	*Operating conditions*	Operation between 15°C and 40°C at an altitude up to 2,000 meters. Extremely low relative humidity to condensing humidity. Result interpretation in average-light settings.	Operation between 10°C and 45°C at an altitude up to 3,000 meters. Extremely low relative humidity to condensing humidity. Result interpretation in low-light settings.
	Sample types	Oral fluid/saliva. Finger-prick whole blood.	Oral fluid/saliva. Finger-prick whole blood. Not to exclude the possibility of other fluids (e.g., urine) if data support use of the sample.
	Method of sample collection	Blood-based samples—finger prick with lancet. Oral fluid-based samples—swab or spit.	Blood-based samples—simple, easy-to-use transdermal collection. Oral fluid-based samples—swab.

Requirement category	Variable	Minimum requirements	Optimistic requirements
Operational requirements	*Sample volume*	Finger-prick capillary blood (maximum 50 μL). Multiple gum swabs or prolonged oral fluid collection (up to one minute).	Finger-prick capillary blood (maximum 10 μL). One swab of gums for oral fluid.
	Sample dilution/manipulation	Minimal sample processing; no more than one operator step. Diluent supplied with kit.	No sample dilution/manipulation or integrated dilution/manipulation.
	Need for a follow-up test	If positive, referral to a health care provider is required.	If positive, referral to a health care provider is required.
	Time to result	20 minutes or less.	5 minutes or less.
	Duration of valid sample (time from taking sample to insertion in device)	Immediate use of sample.	>1 hour (then result gives "invalid" rather than "false" return).
	Duration of valid result	One hour: Results are stable (do not convert from negative to positive) during this time period.	24 hours or longer. Results are stable and do not change. Another option is results are "masked" or destroyed after a specified read time period to ensure privacy.
	Assay control	Procedural control internalized in the cartridge for each individual test.	Control internalized in the cartridge for each individual test (indicating sample adequacy and that the assay was performed correctly).
	Device control	Indicator of instability or expiration.	Indicator of instability, expiration, inadequate sample, and incorrect procedure and/or use.
Kit requirements	*Unit packaging*	All materials required for assay and reagents, including buffers or other consumables to test one self-test user, should be included in an individually packaged, self-contained kit.	Complete, self-contained kit for testing only one user with further simplification by maximizing component integration as much as possible.

Requirement category	Variable	Minimum requirements	Optimistic requirements
Kit requirements	*Unit*	Generic multi-lingual packaging, increased use of symbolic representation versus text, adherence to World Health Organization (WHO)/ Global Harmonization Task Force (GHTF) rapid diagnostic test (RDT)-specific guidelines.	Context-specific, culturally relevant/acceptable packaging. Further refinement, consolidation, and enforcement of WHO/GHTF guidelines.
	Unit size	100 kits/six cubic feet (to be re-evaluated).	150 kits/six cubic feet (to be re-evaluated).
	Cold chain	Stable for 12 months at 2°C to 40°C, 70% humidity, including transport stress (48 hours with fluctuations up to 50°C and down to 0°C).	Stable for 24 months at 0°C to 45°C, 90% humidity, including transport stress (48 hours with fluctuations up to 50°C).
	Cold chain	None required at any point in supply chain or storage.	None required at any point in supply chain or storage.
	Clean water	No water required.	No water required.
	Electrical power	No electrical power required.	No electrical power required.
	Instrumentation/additional third-party consumables	None. Disposable test only.	None. Disposable test only.
	Other supplies	No other supplies other than the bare minimum to perform the test.	No other supplies other than the bare minimum to perform the test.
	Safety precautions (biosafety requirements)	Closed, self-contained system; unprocessed sample transfer only, no open handling of biohazardous material. Biohazard information should be clearly mentioned in instructions.	Closed, self-contained system; unprocessed sample transfer only, no open handling of biohazardous material. Biohazard information should be clearly mentioned in instructions.
	Waste management	Disposal of cartridge in routine waste stream; compostable materials for packaging preferred.	Disposal in routine waste stream; compostable materials as applicable (packaging, etc.).
	Kit quality indicators	Clear, explicit marking with expiration date.	Clear indicators of a "bad" test (exposed to conditions that could compromise test performance, such as age of the test, temperature, humidity, and physical damage).

Requirement category	Variable	Minimum requirements	Optimistic requirements
Commercialization requirements	*Product registration, WHO prequalification, regulatory approval*	Manufactured to current good manufacturing practices (cGMP) standards and specific requirements necessary for legal sale and use in each target country.	Manufactured pursuant to cGMP; ISO 13485 certified and authorized for use by a credible regulatory authority (European Union [EU], FDA), and/or WHO prequalified and registered for *in vitro* diagnostic use, and/or Clinical Laboratory Improvement Amendments (CLIA) waived.
	Target cost per result/end user	Fully subsidized for poor target populations through public clinics. Price to affluent target populations or through private distribution would be country-specific. South Africa: R20-R40 (~US$2–US$4). Kenya: KES 300 (~US$3) Malawi: MK 1000 (~US$2.50) For a non-country-specific estimate, ~US$1.06 per test.	Fully subsidized for poor target populations through public clinics. Price to affluent target populations or through private distribution would be country-specific. South Africa: (R10 (~US$1). Kenya: KES 30–50 (~US$0.30–US$0.50). Malawi: MK 100 (~US$0.25) For a non-country-specific estimate, ~US$0.72.
	Channels to market	Free or nominally priced through public clinics.	Public clinics and multiple private channels to access all key target populations.
	Supply, service and support mechanism	Literature within the test package guiding linkage to care and to help perform/ interpret tests results. Involvement in supply chain development.	Training programs for distributors or direct participation by manufacturers in providing testing help and post-test direction (*not* counseling). Support via phone or SMS. Control of supply chain.
	Quality control (QC)	Key quality systems certifications (ISO 13485) and cGMP practices. Full cooperation with quality assurance (QA) efforts.	Quality systems certifications, cGMP practices. Proactive design for non-ideal handling scenarios. Full participation with QA efforts.

3.0   Annotation

3.1   Context (use case)

3.1.1   Proposed use and value proposition
Minimum requirement
RDT to detect chronic HIV infection in target users

Optimistic requirement
RDT to detect early-stage and chronic HIV infection in target users

Rationale
HIV test intended as an over-the-counter test for consumer use as an aid in the pre-screening, screening, or diagnosis of infection with HIV-1 and HIV-2.

Evidence from literature
Self-testing has the potential to be an innovative component of community-wide strategies for HIV prevention. This testing method could serve populations that do not have access to standard voluntary counseling and testing (VCT) services or do not use facility-based, standard HIV testing because of privacy concerns, stigma, transport costs, or other barriers.[4]
In order to increase global HIV testing rates and to ensure early access to treatment, further exploration of new HIV testing options should be a research priority.[5] The intended use for the rapid diagnostic HIV self-test is to detect early-stage and chronic HIV infections in target users who may otherwise be deterred from current in-country testing services. HIV self-tests that are similar to a pregnancy test and can be used in the privacy of a target user's home or any other place that suits a target user could have the potential to bypass barriers currently deterring people from testing.

Facility-based services are unlikely to fully meet ongoing needs due to major constraints in scaling up HIV testing and counseling. Barriers include the burden of viral load testing, lack of trained staff in resource-poor settings, long wait times in facilities, social stigma and privacy issues, and personal cost involved in accessing testing services.[6-9] In addition, Venter et.al proposed that the paternalistic attitudes of some health workers responsible for providing HIV testing and counseling (HTC) are a barrier to accessing testing which may deter people from seeking testing or re-testing.[10]

It was proposed that HIV self-tests should be widely available and that linkage to care must be locally facilitated. When considering how self-testing could be utilized, Venter et. al suggested three models:[10]

1) Clinically restricted-clinical counsellor model: where HIV kits were given by health workers in specific situations such as part of post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) and given to couples testing and high risk groups.

2) Semi-restricted (public health programmes) model: where HIV ST is linked to other testing programmes

3) Open access model: where this will be part of the progression of "know your status", normalizing HTC to increase the desire for HIVST which could potentially have a large market.

The value of HIV self-testing may engage and empower the target user to have more control over their health.[5]

Evidence from PATH studies
Although key stakeholders stated that HIV self-testing could be an important complement to existing community- and facility-based testing approaches, facility-based services are unlikely to fully meet ongoing need. Responses from key stakeholders corroborated with the literature that there are major constraints in scaling up HTC services. HIV self-testing services have the potential to bypass the obstacles and barriers mentioned above. Respondents felt that HIV self-testing would encourage people to test earlier; knowing an HIV-positive result earlier would allow better planning or protection on the part of the individual.[9]

3.1.2   Target population
Minimum requirement
Persons seeking to learn their HIV status through non-clinic-/non-provider-assisted testing.

Optimistic requirement
Persons seeking to learn their HIV status through non-clinic-/non-provider-assisted testing.

Rationale
The intended target populations are individuals who are untrained lay users who are seeking to learn their HIV status through non-clinic-/non-provider-assisted testing; especially hard-to-reach, at-risk, and vulnerable populations.

Evidence from literature
To expand HIV testing coverage to untested and retesting populations, self-testing could be a very good option to reach those who may otherwise be reluctant to get tested with assistance.[6]
Specific populations mentioned in the literature review include hard-to-reach populations, young people, men, sex workers, men who have sex with men (MSM), adolescents, people who inject drugs, and couples.

Evidence from PATH studies
Common themes emerged with regard to the specific target populations from experts in the field that corroborated the literature review. Self-testing was simply seen as a tool to access hard-to-reach groups and those who are particularly worried about privacy, confidentiality, or stigma.[9]

Using self-testing as the model of choice across all populations was suggested by a small number of respondents, particularly in Malawi where it was suggested that people should be offered the opportunity to use any type of HTC services and that introducing self-testing only to certain sections of the community or key populations would be discriminatory.

South African experts mentioned that middle class and urban populations who are more financially secure and literate may be an ideal population.[11] Middle-income and high-income populations and professionals in the working class also do not regularly visit VCT centers.[11]

3.1.3   Target countries
Minimum requirement
Countries that bear the burden for the HIV epidemic have the highest rates of needed, but unmet, testing and have the health infrastructure to launch HIV self-testing.

Optimistic requirement
All countries.

Rationale
Countries where the HIV epidemic is greatest, especially where access to testing may be limited and/or stigma is associated with accessing current testing services, could benefit from HIV self-testing as an additional modality. Ideally, all persons seeking self-testing should be able to gain access to such tests, independent of their global location.

Evidence from literature
Sub-Saharan Africa currently bears the burden of the HIV epidemic, accounting for 67% of the total 33.2 million infected individuals.[12] In Africa as a whole, it is estimated only 34% of women and 17% of men have ever had an HIV test.[13] Further studies and discussions will need to follow up to understand the health infrastructure and political readiness of a country to launch HIV self-testing in their current health care system.

3.1.4 Infrastructure level
Minimum requirement
Minimal infrastructure sufficient for self-testing in a private setting; no cold chain support, no electricity or clean water requirements.

Optimistic requirement
Minimal infrastructure sufficient for self-testing in a private setting; no cold chain support, no electricity or clean water requirements.

Rationale
The question of where in the health care delivery system a self-test will be used is complex. By nature, most HIV self-testing will fall outside of the current health care delivery system. However, a variety of factors (e.g., counseling, linkage to care, and in some settings such as Malawi, possibly acquiring self-tests) interface with various levels of the health care delivery system. To facilitate access to the desired target population, minimal infrastructure requirements must not deter use in a private setting with no electricity, clean water, or cold chain support.

Evidence from literature
With diseases that carry a stigma such as HIV, HIV point-of-care tests can potentially empower patients to self-test in the privacy of their homes.[14] However, self-tests that are used in a private setting should have minimal infrastructure to run the test. In-home testing for HIV demands the simplest type of device, along the lines of a pregnancy test.[6,15]

Evidence from PATH studies
Experts have varied opinions about self-testing for HIV. Stakeholders expressed some hesitation about the implementation of such changes in the practices for HIV detection in low-income countries where health infrastructure may not have sufficient capacity.[9] However, experts responded that further discussion is needed to understand some of the issues that may come up in private-setting testing. Those issues include increased risk of anxiety, need for counseling that may be bypassed by self-testing, potential coercion in a home-testing environment, and inaccuracy of the test in the hands of the untrained lay user.

3.1.5   Special populations
Minimum requirement
Populations to include persons of low socioeconomic status, women of childbearing-age potential, and specific target groups.

Optimistic requirement
Populations to include persons of low socioeconomic status, women of childbearing-age potential, and specific target groups.

Rationale
To expand HIV testing coverage to untested and retesting populations, self-testing is a good option to reach those who may otherwise be reluctant to get tested with assistance. Ideally, the special populations mentioned below would be targeted to get tested.

Evidence from literature
Specific populations mentioned in the literature review include hard-to-reach populations, young people, men, sex workers, MSM, adolescents, people who inject drugs, and couples.

Hard-to-reach populations: In rural sub-Saharan Africa, poor local access forces many to travel long distances, and current VCT is mainly available from district and provincial hospitals, which deter villagers because of transportation costs.[16,17]

Young people: Globally, only about one-third of young people know their HIV status, which is far below the United Nations General Assembly Special Session target of 95%.[18] Young people fear that attending VCT discloses that they are sexually active to their parents. Moreover, they do not perceive themselves at risk of HIV and reported feeling ill-equipped to deal with the consequences of a positive result. In the South African Youth Survey, 62% of HIV-positive youth reported feeling they had little or no chance of contracting HIV.[19] Sex workers, MSM, and people who inject drugs, who are often at high risk of HIV infection, are also frequently "hidden" populations. To provide HIV testing services to these populations requires innovation such as mobile HIV testing. However, in many settings, access to these "hidden" and often stigmatized populations remains difficult. A deliberate, standardized approach of eliciting information about sexual behavior, drug use, and other potential HIV exposure could increase provision of HIV testing services, but should be implemented with an explicit effort to protect confidentiality, reduce potential negative consequences, and provide high-quality services.[20]

Couples: Approaches to enhance couple counseling include public endorsement by political leaders, national policies such as Zambia's couple testing in antenatal clinics that influence network agents , and home-based HIV testing.[20]

Previous studies have shown that socioeconomic status is one of the most important predictors of whether and where people seek care for illness.[21] Poor populations also face financial obstacles to accessing health services. The PATH study found use of the private health sector for HIV testing and sexually transmitted infection care increases with wealth in some countries, a finding that is consistent with previous findings.[22]

A nationally representative survey showed that 36% of adults had ever been tested (44.2% among women and 27.4% among men), and women of reproductive age, women in urban areas, and wealthier persons were more likely to have been tested.[20,22]

Evidence from PATH studies
Common themes emerged with regard to the specific target populations from experts in the field that corroborated the literature review. Self-testing was simply seen as a tool to access hard-to-reach groups and those who are particularly worried about privacy, confidentiality, and/or stigma.[9] Men should be targeted because they are less likely than women to seek treatment and are not identified through routine testing algorithms. Men were perceived to be more concerned about confidentiality. Key populations—especially MSM, sex workers, and other most-at-risk populations—are reluctant and afraid to seek HTC services in health facilities because of stigma, discrimination, and fear of results. Facility-based testing was described as not being youth-friendly from respondents in Kenya and Malawi. Couples are thought to benefit from self-testing because they were likely to appreciate the opportunity to test together at home.[9]

Using self-testing as the model of choice across all populations was suggested by a small number of respondents, particularly in Malawi where it was suggested that people should be offered the opportunity to use any type of HTC, and that introducing self-testing only to certain sections of the community or key populations would be discriminatory. Malawian experts suggested using self-testing as a model for non-pregnant women, the elderly, professionals, the elite of the society, discordant couples, and mobile populations.[23] South African experts mentioned that middle class and urban populations who are more financially resourced and literate may be an ideal population.[11] Kenyan experts mentioned discordant couples accounted for a significantly larger proportion of new HIV infections. It was also stated that middle-income and high-income populations and professionals in the working class also do not regularly visit VCT centers.[11]

3.1.6   Fit with Clinical Workflow/Linkage to Action (Care)
Minimum requirement
Instructions on next steps and for seeking care based on their test result.

Optimistic requirement
Minimum plus access in-person or live phone-based, SMS or other on-demand mechanism for counseling and referral.

Rationale
Current linkage to care is low because health care infrastructure linking the results of patients to next steps is lacking. Like all rapid HIV tests, a self-test would be a screening or even pre-screening test, so people must be aware of the necessity of further screening and confirmatory testing. Hence, there is a need to develop mechanisms to inform self-testers about, and link them to, further screening and confirmatory testing and promote access to services.

Evidence from literature
Linkage to counseling as well as to treatment and care services remains a major challenge for acceptability of HIV self-testing.[5,24] Previous studies have shown linkage to care is inadequate with low compliance to seek care. In a recent systematic review of 28 studies, the median proportion of patients who were followed after they were tested for HIV until they were tested for the clinical status of their disease by first CD4 count or clinical staging was 59% (95% confidence interval [CI]: 35–88). Similarly, only about half of HIV-infected persons who received home-based testing in Kenya reported to an HIV clinic within one month.[20]

It is essential to link HIV self-testing to adequate counseling and support services.[5] HIV self-tests should link the patient with details of follow-up support within the health care system in-country. It is important to develop mechanisms to inform self-testers about the necessity to seek further screening and confirmatory testing, partner notification, and to promote access to services.[4,24] The messaging and

information required to link patients to counseling and follow-up testing may be highly variable due to language, culture, and context of use for each country.

Companies should follow a model similar to the OraQuick® model. The company provides a comprehensive customer website and a toll-free phone number for customer support. The "live" customer phone support is available 24 hours a day, every day. The bilingual (English or Spanish) customer service representatives can help answer questions about HIV and AIDS. In rural areas with limited telephone access, group information sessions and close links to on-site social organizations could be a possible counseling and support strategy for self-testers.[5,24]

Studies are needed to discover whether potential users understand the potential for false positive and negative results and the need for follow-up with further screening and confirmatory testing.[4,25]

A systematic review of retention in care between testing and treatment in sub-Saharan Africa estimated that less than 20% of tested patients completed all the necessary steps in the care cascade. Beyond making care accessible, the next phase of self-testing feasibility studies must evaluate the completion of the care cascade from testing to treatment to demonstrate true self-testing success. The completion of a testing program—its effective successful ''endpoint'' of diagnosing a previously unidentified case—is not only documenting that the patient received the appropriate result, but also that the positive result ignited a cascade of events leading to timely and effective access to HIV-related care.[26]

There is a need for innovation and improvement in the effectiveness of counseling methods regardless of the HIV testing method. In the context of self-testing, new approaches to pre-test and post-test counseling should be developed and evaluated for appropriateness, feasibility, and effectiveness. These might take the form of picture-based or word-based brochures tailored to local literacy levels that would be included with the HIV self-test kits, telephone counseling provided through a toll-free number, tape cassettes, group counseling, or public health kiosks with computer-based counseling placed in high-traffic areas.[4]

Evidence from PATH studies

Users need to be made aware that a self-test is only the first step in accessing health care and that a confirmatory test is needed. One of the most significant concerns raised by the experts was linking self-test users to appropriate counseling and care to ensure that confirmatory tests and follow-up services were offered.[9] Counseling experts were aware that counseling services and toll-free numbers were available in other countries but were concerned that these models from other settings would not be transferrable to their own setting and may be too expensive. Experts from all three countries cited that counseling for reducing the risk of suicide, the need for confirmatory tests, information about treatment services, and the need to inform and educate users about the seroconversion period, including when a repeat test should be performed, needed to be addressed. Outside of telephone helplines, respondents suggested health service announcements, HIV support groups, and group pre-test counseling. Experts in all countries agreed all test instructions must be clear with a step-by-step guide and must state a helpline number that is free of charge that would reassert that a confirmatory test is essential.

In Kenya and South Africa, respondents talked about the need to carry out educational media campaigns (e.g., on local radio and television). Such campaigns could inform the public that self-tests are available, as well as provide information about what and where support is available and what steps should be taken after the test is done.

3.1.7   Data handling

Minimum requirement
Developed communication system that will instruct target users on linking and reporting HIV self-test results with appropriate care (follow-up testing and counseling).

Optimistic requirement
Developed communication system that will instruct target users on linking and reporting HIV self-test results with appropriate care (follow-up testing and counseling. Additional work may be required to define additional optimal requirements.

Rationale
There is a low linkage to care and low understanding of the next steps for results. Countries need to invest in the infrastructure and communication system that will instruct users on how to report their HIV self-tests.

Evidence from literature
The most critical elements of point-of-care tests are rapid turn-around and communication of results to guide clinical decisions and completion of testing, and follow-up action at the same clinical encounter.[15] Data handling of results at the peripheral laboratory level and hospital/clinic level have shown to be a poor process. Previous studies have shown poor data handling at the peripheral laboratory level for laboratory results because there is no link between laboratory information systems and hospital systems detailing clinical information. Laboratory interpretation of results can be extremely difficult because of the lack of clinical information that accompanies the samples. In general, this is a weakness of national programs, in which all laboratory results can be collected and audited but cannot be matched to clinical outcomes.[8]

HIV self-testing is so far only linked to counseling telephone hotlines. However, especially in developing countries, telephone hotlines do often not seem to cover clients' needs when it comes to notification of results and adequate post-test counseling. Furthermore, an evaluation of barriers to point-of-care testing for infectious diseases in low- and middle-income countries from Pai et al cited that the most critical elements of point-of-care testing are 1) rapid turn-around and the communication of results to guide clinical decisions, and 2) completion of testing and follow-up action in the same clinical encounter.[15] If systems for reporting results are not linked to a treatment or counseling plan, test results, even if rapid, are unlikely to have a clinical or public health impact. Further discussions will be needed to develop a communication system for the target lay user to report results and follow up with linkage to care and counseling. The development of accessible communication systems needs to be secure to ensure patient confidentiality.[27]

Evidence from PATH studies
Linking testing to counseling was cited as a significant challenge for self-testing. The greatest risk of self-testing was the difficulty in providing users with pre- and post-test counseling services and, in the case of positive results, ensuring that confirmatory tests and follow-up services were offered.

3.1.8   Analyte

Minimum requirement
Qualitative detection of HIV infection; antibody.

Optimistic requirement
Qualitative detection of HIV infection, antibody, biomarker, and nucleic acid.

Rationale
HIV point-of-care tests have traditionally been designed to detect antibodies. This strategy is successful for most of the population, but additional sensitivity may be required for different populations or use scenarios. Other uses could benefit from the detection of HIV biomarkers or nucleic acid, possibly as multivalent detection technologies.

Evidence from literature
Current rapid HIV tests support qualitative detection of antibodies against HIV. State-of-the-art, laboratory-based testing also utilizes biomarkers and nucleic acids to diagnose HIV infection. Translation of these analytes to point-of-care testing could advance the field, but is not required to have an immediate impact.

Evidence from PATH studies
Lay users involved in the PATH-sponsored usability study in Kenya, Malawi, and South Africa had the opportunity to use five different HIV self-tests. While most untrained users correctly interpreted strong positive and negative results, we found that a non-trivial portion of users interpreted results incorrectly. Additionally, weak positives proved difficult to interpret. While current HIV rapid tests are qualitative in nature, the intensity of the test line often correlates to the quantity of the analyte (antigen or antibody) in the sample, meaning that seroconverters or individuals who are immune-compromised may ultimately show weak positive results on these tests.

3.1.9   Platform/methodology
Minimum requirement
Immunochromatography or immunofiltration.

Optimistic requirement
Immunochromatography, immunofiltration, microfluidics, or other.

Rationale
Currently immunochromatography and immunofiltration platforms are available for point-of-care testing. These platforms are well suited for self-testing, but additional platforms could be utilized. Any platform for self-testing needs to be able to stand alone and must be easy to use.

Evidence from literature
Immuncochromatography and immunofiltration have proven to be effective, rapid point-of-care test platforms. Other platforms, such as microfluidics, patterned paper networks, non-instrumented nucleic acid detection, etc., show potential utility in this space and could be developed into a self-testing platform.

Evidence from PATH studies
Lay users involved in the PATH-sponsored usability study in Kenya, Malawi, and South Africa had the opportunity to test five different HIV self-tests, with four of the five tests based on a lateral flow strip test platform, and the additional test was on a flow-through test platform. Platforms with familiarity to users are potentially advantageous. PATH has conducted other evaluations and has relationships with technology developers and manufacturers that indicate new platforms that could be suitable (or be modified to be suitable) for self-testing may be on the mid- to long-term horizon.

3.2   Performance requirements

3.2.1   Precision/concordance
Minimum requirement
Precision is not applicable but concordance to a predicate test should be greater than 99%.

Optimistic requirement
Precision is not applicable but concordance to a predicate test should be greater than 99%.

Rationale
A high standard of reproducibility that will help build consumer trust in product reliability is critical. Invalid RDTs result in growing distrust and frustration. The best metric for demonstrable reproducibility is concordance against predicate devices, not precision.

Evidence from literature
Since rapid testing is a qualitative, binary result, a quantitative determination of precision cannot be made. However, concordance to a proven standard affords a sense of testing confidence/repeatability. Jackson et al published a comparison of test results from rapid tests (SD Bioline and Sensa) to laboratory-based ELISA testing. Of the 3,986 matched samples, the results were in concordance with the laboratory results in the vast majority of cases (99.4%).[28]

Reproducibility over time is not reported in the literature. However, using a blood panel of contrived blood specimens, the OraQuick ADVANCE® Rapid HIV-1/2 label states a 100% reproducibility at three sites, using three device lots, on three different days by a total of nine operators.[29]

Pant Pai et al, note the inherent variability in disease progression between individuals resulting in differences in immunological responses and, hence, the variable window to allow for seroconversion. In fact, Pant Pai et al suggests that this may be a reason for false negative test results, and most were related to the weakness of the test itself: the lack of antigen prevents the identification of an undiagnosed HIV infection.[30] Therefore, reproducibility testing may be an inherently poor indicator of quality.

Evidence from PATH studies
Our usability studies did not evaluate test performance in result accuracy. However, on the basis of our literature review, 99% concordance to current reference tests (i.e., fourth-generation laboratory tests) must be reached.

3.2.2   Clinical sensitivity and specificity
Minimum requirement
Sensitivity >99%; specificity >98%.

Optimistic requirement
Sensitivity >99%; specificity >99%.

Rationale
For the purpose of this target product profile, clinical sensitivity and specificity refer to the performance of the test with well characterized (retrospective) clinical samples in a controlled (laboratory) setting conducted by trained personnel. This is not a substitute for field performance testing (unsupervised HIV self-testing), addressed in section 3.2.5. Clinical sensitivity and specificity need to be adequate in order to achieve the goals of HIV self-testing of an HIV-prevention program. In order to achieve the field performance requirements, high quality, reliable tests are essential, as the performance will only decrease

in conditions that are less than ideal and with untrained users. Controlled testing provides a baseline for test performance.

Evidence from literature
The evaluation program developed and implemented by WHO requires performance equal to or greater than 99% sensitivity and 98% specificity with well characterized samples in a controlled testing environment.[31-37]

Interestingly, the product label of the OraQuick ADVANCE® Rapid HIV-1/2 states a device sensitivity for oral fluid samples of 99.3%, (95% CI: 98.4–99.7) and a specificity of 99.8% (95% CI: 99.6–99.9). For blood fluid samples, device sensitivity 99.6%, (95% CI: 98.9–99.8) and specificity 99.9% (95% CI: 99.6–99.9).[29] In contrast, in a systematic review of studies utilizing OraQuick ADVANCE® Rapid HIV-1/2, Pant Pai et al determined that the sensitivity is approximately 2% less in oral mucosal transudate than finger-stick specimens, and specificity is approximately equivalent between oral or plasma specimens. According to Pant Pai et al, ideally a very high or perfect (100%) sensitivity is desirable but difficult to achieve.

Evidence from PATH studies
Our laboratory studies used seroconverter, low titer, and contrived weak positive samples to assess the performance of several rapid tests. Our results were biased toward these low positives. The WHO model for evaluating HIV test performance is thorough and should remain as a standard of test performance.

3.2.3   Analytical sensitivity and specificity
Minimum requirement
Sensitivity >97%; specificity >97%.

Optimistic requirement
Sensitivity = >99%; specificity = >99%.

Rationale
These metrics provide a baseline understanding of an assay's capabilities, establishing the smallest amount of detectable analyte (analytical sensitivity) and level to distinguish between closely related analytes (analytical specificity). The metrics are measured in laboratory or controlled conditions and use quantitated reference samples. This parameter is most meaningful for tests that test for nucleic acid (copy number) or protein (concentration). Analytical sensitivity is difficult to measure for antibody detection tests and is therefore less meaningful. Analytical sensitivity and specificity percentages are relative to each individual product claims. Each target will have specific clinically relevant endpoints.

Evidence from literature
The US Agency for International Development (USAID) and US Centers for Disease Control and Prevention (CDC) also instituted a vigorous test kit validation program in 2006, so that users in US President's Emergency Plan for AIDS Relief (PEPFAR)-supported countries could have access to rapid testing kits that are not yet FDA approved but meet the performance criteria. This evaluation is performed at the CDC using a well-characterized global panel of serum and plasma specimens obtained from several countries with diverse HIV-1 subtypes and HIV-2. Criteria for acceptable performance are a sensitivity of 99% or more and a specificity of 98% or more.[38]

Evidence from PATH studies
Our usability and laboratory studies did not evaluate analytical sensitivity or specificity.

3.2.4   Reference method
Minimum requirement
Days before Western Blot (WB) positive: 0
Days since Nucleic Acid Test (NAT) reactive: 24

Optimistic requirement
Days before WB positive: 25
Days since NAT reactive: 0

Rationale
A successful self-test RDT must possess good correlation with a well characterized reference method that is proven useful in diagnosing HIV. Western Blot and NAT have been historically used in diagnosing HIV infections and represent two ends of a broad spectrum of tests available. As WB testing is conducted less frequently and is generally seen as a waning technology, we present both WB and NAT as references. The optimistic HIV self-test would be as sensitive as NAT, reducing the window period. The minimum is to match performance of currently available rapid tests, which approximate WB.

Evidence from literature
It is not necessary for HIV self-tests to be as sensitive as NAT, nor as specific as WB, but rather well characterized as to how they perform relative to either or both of these methods. The performance of current HIV rapid tests has been well documented relative to WB positivity. As NAT has become more accessible, second, third, and fourth generation HIV tests have been characterized to it as a standard.[39-41] As a reference, the most advanced antigen/antibody laboratory tests are fourth-generation HIV assays that have the ability to detect antibodies to HIV-1/2 and p24 antigen simultaneously, which reduces the window period to approximately 7 days since NAT reactivity (or approximately 20 days before WB positive). Fourth-generation ELISA assays demonstrate very high sensitivity (100%) and specificity (99.5%).[42]

Evidence from PATH studies
PATH studies did not specifically investigate the use of particular standards, but samples used in laboratory evaluation of prototypes support using either WB or NAT as an anchor and calculating days from the reference method to test positivity.

3.2.5   Field performance
Minimum requirement
In the context described in section 3.1, the test should achieve>70% sensitivity and >90% specificity.

Optimistic requirement
In the context described in section 3.1, the test should ideally achieve>90% sensitivity and >98% specificity.

Rationale
Clinical sensitivity and specificity need to be adequate in order to achieve the goals of HIV self-testing of an HIV-prevention program. It is likely that this will be context-specific. Positive and negative predictive values (additionally driven by disease prevalence) can impact a wide range of important issues from policy to public opinion. The highest sensitivity and specificity are always preferred, but realistic expectations must be made of technologies and how they fit within use case scenarios. An assumption is made that users (and healthcare professionals and policy makers) would prefer a test with a positive predictive value greater than chance (>50%). Additionally, errors committed by users (e.g. sample

collection, conducting all steps accurately, interpreting results) that impact device sensitivity and specificity will inevitably occur.

In conducting a basic sensitivity analysis, lower sensitivity (70%) may be acceptable, but must be accompanied by higher specificity (>97% in a population with 6% disease prevalence) in order to achieve 60% positive predictive value and >98% negative predictive value. Sensitivity of 85% and specificity of 90% in a population with extremely high prevalence (15%) would result in 60% positive predictive value and >97% negative predictive value.

The trade-offs with lower sensitivity and specificity (and thus high numbers of people getting false results) has impacts on public health (unknown positives not seeking care, and people with false positive results seeking care, potentially adding to the burden of the health system) have to be carefully weighed before advancing an HIV self-test to implementation.

Evidence from literature
In 2012 the FDA Blood Products Advisory Committee (BPAC) recommended minimal acceptance standards of performance of 95% sensitivity and 95% specificity.[43] This was not achieved for OraQuick, but the product was approved with lower sensitivity, based on modelling that took into account likely test users, HIV prevalence, and the number of infections that could be averted.

Little is published on the acceptable positive and negative predictive values of self-tests, but in certain populations when testing is conducted by a healthcare professional, the positive predictive values can be high.[35,36,41,44]

Tests must be robust, with a wide range of usage and users, in order to gain market trust and increase testing coverage. Tests should also have low rates of "invalid" results across a wide range of acceptable operating temperatures to facilitate use of outside temperature-controlled laboratories.[45] While on-market HIV RDTs generally have high sensitivity and specificity, two studies suggest field performance for HIV RDTs is unacceptable.[46,47] Moodley et al looked into four HIV RDTs, all of which claimed to meet international standards of at least 99% sensitivity and 98% specificity. None of the four HIV RDTs met the international standards.[46] Use of the OraQuick ADVANCE® Rapid HIV-1/2 in field trials in Malawi resulted in overall sensitivity for self-test; self-read was 97.9% with specificity of 100%.[6]

Evidence from PATH studies
While our usability studies did not evaluate test performance on the basis of literature review and field usability studies, usage of self-tests by untrained lay users may likely result in lower sensitivity and specificity than the Moodley and Plate studies involving trained health workers or the Choko studies by *trained* lay users. In the PATH usability study lay users generally showed a poor ability to conduct all steps of all provided tests correctly.[48] The most significant difficulty was in sample collection, regardless of whether the user took blood or oral samples. Problems involved use of lancets, correct sample quantity, and transfer of sample.[48] Lay users also made errors as a consequence of misunderstanding instructions, and some noted that instructions were not clear.[49] For example, 39% of the participants conducted the oral test correctly. Some used the wrong end of the oral collection swab, some performed incomplete swabbing or dipped the swab into test liquid before swabbing the mouth.[48] Some participants were confused by the word "swab":

> *"Eh It was difficult because I couldn't understand the word "swab," I couldn't understand what was required of me… the word swab doesn't make sense to me…I did [sample collection] according to the instructions, like touching my teeth, yes and the gums like it is written touch it even in the tongue like it has been explained."*[49]

One third of the participants used test liquids incorrectly. This error could have been a result of misinterpretation of instructions and/or difficulty in opening test liquids. Five participants spilled test liquid when they tried to unscrew containers that had pop-up caps. For one test prototype, test liquid is delivered by pushing the test into a sealed cap, thereby eliminating the need to open the container and count drops. Almost half of the participants (42%) were observed not pushing the test enough to break the seal and adequately introduce enough test liquid.[48]

3.2.6 *Rate of errors in device interpretation*
Minimum requirement
Correct interpretation rates: 98% for negative, strong positive, and invalid; 95% for low positive.

Optimistic requirement
No interpretation needed.

Rationale
The device must provide an unequivocal result to minimize the chance of result misinterpretation.

Evidence from literature
In the case of self-testing, or any rapid diagnostic, the prevalence of weakly reactive lines is the major cause of poor result clarity and therefore leads to interpretation errors (namely false negatives) by the end user. Furthermore, the inability to clearly interpret results leads to results that may conflict with confirmatory testing, creating indeterminate results. While indeterminate results can be caused by the user,[30] the manufacturer must minimize, if not eliminate, weak lines caused by the device. Pant Pai et al attributed false negatives to the device itself when most were related to the weakness of the test itself: the lack of antigen prevents the identification of an undiagnosed HIV infection.[30] The common occurrence of weak lines of reactivity was a source of false-positive and false-negative interpretation errors expressed by several technical advisory group members,[50] and a challenge was "for participants to properly conduct the test and obtain the correct result; and timely access to a health care system."[26]

Evidence from PATH studies
In the PATH usability testing, lay users evaluated cards depicting possible result scenarios: positive, negative, weak positive lines, and invalid results. Strong positives, negatives, and weak positives were correctly identified 79%, 80%, and 27% of the time, respectively. Invalid results —either no lines or a positive line but no control line—were correctly interpreted 81% and 67% of the time, respectively. These results demonstrate a need for improvement. One prototype that did not clearly mark the locations of control and test lines showed the lowest frequency of correctly interpreted negative results at 48%, with invalid results without control line at 41%. In contrast, another prototype, using different symbols for control and test line locations, resulted in the highest percentage of participants (91%) correctly identifying the result.[48]

3.2.7 *Device failure/invalid rate*
Minimum requirement
Device failure and invalid rate less than 5%.

Optimistic requirement
Device failure and invalid rate less than 1%.

Rationale

Failure rates must be extremely low to prevent erosion of market and clinical confidence. This includes manufacturing flaws that cause the device to fail as well as invalid tests caused by user errors. OraSure, in early clinical phase trials reported a 5% test system failure rate and later achieved 1% test system failure rate with later clinical phase trials.[43]

Evidence from literature

Test failure or invalid test results lead to repeat testing and can also lead to frustration, loss in product confidence, and time wastage on the part of patients, community health workers, and clinical staff; this is particularly more acute in busy, overburdened clinic settings.[50-53] At a population level, approximately 5% of patients with reported indeterminate or discrepant results are HIV infected, and indeterminate results during pregnancy remains a challenge. The public health significance of these indeterminate or discrepant results is the possibility of acute HIV infection after diagnosis.[20]

Test failure or invalid results can be due to suboptimal QC at the manufacturing level or operator error. Defective kits, with issues such as dual reactivity, are indicative of potential manufacturing problems. Several rapid test kits claim to discriminate HIV-1 and HIV-2 infections, but dual reactivity is common. Misclassification can occur due to significant antibody cross-reactivity with viral antigens between the two HIV types, thus singly infected persons could be misdiagnosed as having dual infection.[38] Another issue is that production variability may arise if a product is made at different locations.[38]

Product selection criteria for HIV rapid tests set by WHO requires that tests perform with an invalid rate equal to or less than 5%.[37]

Evidence from PATH studies

The PATH usability studies did not evaluate test performance. However, device failures were observed due to components that were easily broken or steps/procedures that were difficult for the user to follow/conduct.

3.2.8   User-induced failure rate

Minimum requirement

User failure less than 20%.

Optimistic requirement

User failure less than 10%.

Rationale

Minimum and optimistic cutoffs were based on the PATH field studies but to be used only as a starting point. PATH field studies demonstrate that user mis-use of the device would potentially result in high failure and invalid rates. In contrast, in OraSure's presentation of results to BPAC, a remarkable 25 subjects out of 5,662 subjects (0.4%) could not run the test whether by operational error or by other unnamed reason. Since the OraSure subject pool was largely consisted of individuals who completed at least high school (approx. 80%), we hypothesize that a higher user error would be found in low resource countries due to a greater uneducated target population.

Evidence from literature

In a study of more than 300 HIV-negative users of the Determine® fourth-generation antigen/antibody RDT, only 8% failed to achieve a valid test result compared to 56% of users who produced invalid results in a separate study reported by Lee et al.[54] Pant Pai et al attributed false positives to several factors, including errors in test performance and conduct of the test (i.e., inaccurate specimen collection, gum

swabbing more than once), and errors in the interpretation of results (interpreting weakly reactive lines). Indeterminate test results were a direct effect of suboptimal training of counselors, and lapses in QA.[30] Tests should be robust, with low rates of invalid results across a wide range of acceptable operating temperatures to facilitate use outside temperature-controlled laboratories.[45]

Evidence from PATH studies
The PATH usability studies underscored several user-based causes of error; primarily in areas of 1) sample collection, 2) sample transfer, and 3) buffer addition, for all five self-test prototypes. User errors were recorded in all test steps and each test prototype. Less than 25% of all participants conducted all steps correctly and 47.3% of participants performed more than on error.[55] The more complex a test is, including number of components and steps, the likelihood that the user will conduct an error is increased. Some of these user-errors have the possibility of the user receiving an incorrect result.

Prototype	O1	FS1	FS2	FS3	FS4
N	33	29	29	30	29
Sample type	Oral	Blood	Blood	Blood	Blood
	n (%)	n (%)	n (%)	n (%)	n (%)
Collected sample correctly	13 (39.4)	14 (48.3)	17 (58.6)	9 (30.0)	17 (65.4)
Transferred sample correctly	N/A	7 (34.5)	N/A	17 (58.6)	12 (41.4)
Added test liquid correctly	28 (84.9)	16 (55.2)	17 (58.6)	6 (20.0)	12 (41.4)

For example, users who correctly performed sample collection ranged from 30% to 65% depending on the test prototype.[48] Therefore test failure or invalid results could potentially start right from the beginning with difficulties obtaining the sample. This indicates a need for test a design that minimizes user errors in these test procedures.[55]

3.2.9   Interferences
Minimum requirement
Low risk of interferences.

Optimistic requirement
No risk of interferences.

Rationale
Self-testing takes place outside controlled laboratory environments. Minimizing any interferences leads to more successful and accurate testing.

Evidence from literature
This is a complex issue that has not been adequately investigated. Adding to the complexity is the fact that interferences may be test specific. Several interfering factors that have been reported and may warrant further evaluation include natural assay inhibitors in the samples, specimen contamination, and environmental factors such as dust and wind.[56-58]

Evidence from PATH studies
No further evidence from PATH Studies.

3.3   User requirements

3.3.1   Instructions for use
Minimum requirement
Pictorial instructions clearly detailing all test components and steps.

Optimistic requirement
Pictorial instructions with text targeted to a fifth-grade reading level; text available in English and local language(s). All test components and steps need to be clearly detailed.

Rationale
HIV self-tests will be used by target populations with a wide range of characteristics that can influence how the test is conducted. The test must perform well with populations with varying literacy and education levels, as well as experience and comfort with following steps to conduct a test.

Evidence from literature
The most effective strategies to address user-related hazards in the premarket setting focus on improving the actual design of the device's user interface. To the greatest extent possible, the user interface should convey the correct operation of the device through appearance and operation ("look and feel") so that safe and effective use is intuitive and needs little interpretation.[59-61] However, tests are not always able to achieve this goal of intuitive and understandable design. Instructions, labeling, and training can influence users to use devices safely and effectively and are critical usability considerations for safe device use. Still, instructions and labeling rely on the user to remember or refer to the information; hence, these approaches are less effective than modifications to the design of the user interface. In addition, training may be inconsistent or unavailable.[62]

Because many current HIV self-tests are intended for use by health professionals, there needs to be careful modification of labeling and instructions specifically for lay users.[54] Literacy rates of target populations must be considered. Primary level (sixth grade) or lower is the recommended reading level for health information with WHO job aids developed according to this guideline.[56,59] Clear, understandable, pictorial instructions that match the actual dimensions and look of the device (for example, shapes of the test and test wells) are important and can help to overcome literacy and language challenges. Steps that must be done by the user must be described pictorially and graphically, and must be culturally tested.[63] Job aids can improve accuracy of test conduct among health personnel with minimal training,[63] suggesting that even for health workers, instructions for use (IFU) must be simplified and clearly presented.[63]

Evidence from PATH studies
The PATH study findings underline the importance of carefully developed instructions that are tested with the intended user population as well as clear labeling of all components.[48] Key informants from all three countries strongly agreed that instructions need to be clear to accommodate poor literacy. Every step needs to be detailed with both text and images. In addition, people need to know how they benefit and when and how they use the test. External support, such as a helpline number should be provided free of charge.[9]

From lay-user studies, we learned the following specifications. One-page instructions are very desirable, rather than multi-page, since some participants missed the second page of instructions.[64,65] Many participants indicated that they used the pictures to do the tests. Some used the English or local language instructions, while some used both languages. Ideally all three (pictures, English, and local language) would be included. In addition, the font size of the text needs to be large enough to be easily read.[49,64,65]

All components in the test kits and test steps should be clearly and simply described and labeled in the IFU, both with pictures and words.[9] Other suggestions included indicating the function of each item in the kit and numbering components to correspond with test instructions.[48] In the PATH study, a number of participants sought to use the unlabeled desiccant/preservative in their testing procedures by, for example, adding it to the buffer. Participants also commented that the bandage/plaster included in the kit was not labeled with IFU, and this caused some confusion.

Wording used to describe test components and instructions needs to be vetted sufficiently in the local community. Wording not commonly used by lay users or borrowed from English caused confusion (e.g., "cartridge"). "Swab" meant "cotton swab" to a number who were unable to identify the oral collection device as a swab.[49,64,65] Participants felt that some test steps needed more detailed description in the IFU, especially sample collection: how to use the lancet, collect the sample, and add sample to the test. Multiple steps (e.g., swabbing different parts of the mouth or activating the lancet) need to be detailed clearly and in sequence. In particular, instructions on how to use the single-use lancet could be greatly improved. Most participants indicated that they expected to be able to see the needle of the lancet and unintentionally triggered the lancet in their attempts. More detailed instructions on the actual mechanics of the lancet may increase usability.[48,49,64,65] All steps through disposal should be depicted pictorially and with text.[48,49,64]

3.3.2   *Result interpretation*
Minimum requirement
Clear positive, negative, or invalid result with minimal instructions for interpretation. Instructions for interpretation clearly match actual.

Optimistic requirement
Results that can be interpreted correctly without instructions.

Rationale
Reading results correctly is a critical step to enable the user to follow up appropriately and not be misled by incorrect results interpretation. Users must be able to interpret test results correctly with a small margin for error.

Evidence from literature
The frequency with which a person conducting the test interprets the device correctly (the result they receive is what the device indicates) is the benchmark for accuracy as outlined by the FDA BPAC for OraQuick®.[43] Psychological consequences of incorrect test results are of concern and may be more severe when the self-tester receives the result alone. False-positive results can cause psychological stress, and false-negative interpretation may result in a false sense of security with continued high-risk behavior. Hence, correct interpretation of self-test results is of particular interest for self-test design.[4,66]

Literature and evidence regarding HIV self-testing is still limited, but some lessons from other types of self-tests are transferrable to HIV. A systematic review by Ibitoye et al looking at HIV and non-HIV unassisted home tests found that users generally can use and interpret home tests accurately, though they may have great difficulty performing blood-based home tests compared to tests that use other biological specimens (e.g., oral tests).[24]

Users of various home tests were generally able to interpret their test results correctly, expressed confidence in their interpretations, or thought results were easy to interpret. However, some studies also reported challenges in conducting the test due to result interpretation.[24] In a study in the United States with 240 HIV-positive individuals, the concurrence with laboratory-tested results was 94% for oral fluid

and 95% for finger-prick specimens. Post-test debriefing revealed that most clients who made mistakes in test interpretation had not read the instructions and admitted to guessing the result.[67] Studies show that users may inaccurately interpret their own result even if they perform the rest of the test correctly. In Singapore, 12% of participants conducting an HIV self-test did not correctly identify results.[66] In a study in Spain, a high percentage of HIV-negative people who conducted an HIV test were able to perform a blood-based point-of-care test and read the result correctly. However, 8% did not achieve a valid test result, and about 5% of test results were interpreted incorrectly.[54] Most participants (79%) taking HIV home tests in Singapore[66] indicated they were aware that confirmatory testing and follow-up are the next steps upon receiving positive results. Otherwise few home-testing studies reviewed by Ibitoye directly assessed the users' comprehension for the of need for follow-up testing to confirm positive positive results from home tests.[24]

Evidence from PATH studies
Weak positives can cause problems with interpretation since a result with colored lines that are not strong may result in doubt by the user. Discrepant results (e.g., a positive, then negative, then positive result received in algorithm testing) also cause discomfort and doubt. Stakeholders reported stories of clients who tested positive (in facilities) and then were tested again in another setting or at another time and were found to be negative likely due to weak positives and discrepant results received in algorithm testing.[68] In the PATH lay-user studies, negative and strong positive results were identified correctly; however, weak positives were only correctly identified as positives by 26.7% of participants. Interpretation of weak positive results needs to be improved by technical solutions, such as signal amplification, to allow for clearer results presentation. Clearer instructions, images, or other instructional methods are also important to avoid false negatives.[48]

Frequencies for correctly interpreting results were lower than frequencies of participants feeling confident they had performed and interpreted the test correctly. This could potentially lead to self-testers believing in error that they have conducted the test and interpreted the results correctly.[48] In Malawi, most participants expressed that it was easy to read results. However, a number had problems reading results correctly. Contributing factors included unfamiliarity of test result formats, use of short-cuts, and preconceived ideas. Some participants indicated they did not follow instructions and used prior knowledge from VCT services to interpret results.[48,49,64] Tests with three lines (control, HIV-1, and HIV-2) presented interpretation difficulties. Some participants mentioned their perception that one test line indicates a negative result, two lines indicate a positive result, and three means the person is very ill. A test that did not label the locations of the test and control lines on the cassette had the lowest frequency of correctly interpreted negative results (48.3%).[48] While some participants indicated confusion about results presented as dot and line,[48,64] the highest percentage of participants (90.8%) correctly identified results presented with different symbols for control and test lines.[48]

3.3.3   Result presentation
Minimum requirement
The result can be read with the naked eye or with an integrated reader. Result wells should be clearly labeled and/or not require much instruction or explanation to interpret. Test and control lines are easily distinguishable.

Optimistic requirement
Results are presented in a manner that is self-explanatory and needs little or no instruction or explanation to interpret. No weak color lines (and only strong results).

Rationale

The manner in which results are presented can heavily influence a tester's ability to interpret results correctly.

Evidence from literature

Result display and interpretation is key to the user obtaining an accurate result. Test results should be easy to interpret and need minimal, if any, instructions or training to understand. Equipment that is integrated, or not required, is best to decrease errors and cost of the test.[56] The need for additional equipment (e.g., a separate reader) may be a further barrier for expanding testing.[66]

Self-tests should be accompanied by simple, written instructions for interpretation of results. In addition, methods for interpreting the result need to be developed and tested for people who are illiterate or with low literacy levels.[4] Instructions for reading results need to be developed and tested for understanding, including for various literacy levels.[4,45,48,49] In Zambia, a study with community health workers conducting malaria tests suggested test instructions do not sufficiently emphasize the importance of waiting the required time for the test results.[63] In the same study, community health workers who were not trained in reading results frequently read faint positive or invalid tests as negative. Training and job aids, together with instructions to recognize faint results, increased the ability to correctly read results more than instructions or job aids alone.[63]

Ambient lighting conditions or poor eyesight may compromise the ability to distinguish faint positive from negative results, even after instruction. A few studies have shown poor visual acuity and limited ability to afford glasses at a population level in sub-Saharan Africa.[63] Hence, test results must be presented clearly due to these significant problems.

Evidence from PATH studies

In the PATH studies, stakeholders in all countries agreed that tests need to be accurate and involve little risk of misinterpreting results.[9] Some stakeholders suggested HIV self-tests could have a built-in timer that beeps when the test is ready to read and, hence, minimize potential for user error.[48,49] As presented under result interpretation (3.3.2), some participants mentioned their perception that one test line indicates a negative result, two lines indicate a positive result, and three means the person is very ill. Tests with three lines (control, HIV-1, and HIV-2) presented interpretation difficulties. A test that did not label the locations of the test and control lines on the cassette had the lowest frequency of correctly interpreted negative results (48.3%).[48] While some participants indicated confusion about results presented as dot and line,[48,64] the highest percentage of participants (90.8%) correctly identified results presented with different symbols for control and test line.[48] Results presentation that is clear and distinguishable is easiest to interpret.

3.3.4   Level of complexity

Minimum Requirement

Low number of test steps (e.g., three to five) that are easy to conduct.

Optimistic

One easy and intuitive operator step (not timed), excluding waste disposal.

Rationale

Increased number of test steps increases the opportunity for user error. Steps that are reliant on the previous step make it difficult for the user to recover from errors. Even with minimal number of steps, test steps still must be simple to follow and conduct.

Evidence from literature
Point-of-care tests must be simple to perform and interpret by personnel with little to no scientific training.[45] Test kits should be selected based on additional criteria, such as ease of use and interpretation as well as storage requirements, and amount of waste generated.[38] Future test designs should enable easy use across all ages and educational levels.[66] In a study in Singapore, most participants found the kit easy to use, but 85% failed to perform all steps correctly, resulting in 56% with invalid results. In addition, 35% of participants failed to prepare the test kit correctly, and 79% failed to perform blood sampling and transfer correctly.[66]

Evidence from PATH studies
Key informants in all three countries expressed desirable test characteristics as easy to use with very few steps.[9] Some informants suggested no more than five steps with many suggesting three or four steps as a maximum. Most participants shared the view that more steps increases test complexity.[11] Both oral and finger-stick tests were considered acceptable and feasible by lay users to use as part of unsupervised HIV self-testing. Both types of tests required significant adaptation of test instructions. In addition, error rates of sample collection and transfer for oral and finger-stick tests were lower for tests that required separate steps (30.0% to 48.6%). Correct sample collection was higher (58.6%) for tests that had sample collection integrated into the device. However, participants perceived oral tests (with three steps) as less difficult to perform.[48] The lay user study corroborates other study results[54,63] in finding that integrating some of the steps involving sample volume measurement with sample transfer (into the test cassette) increases the opportunity for the naïve test user to conduct the steps properly. Hence, integrating and decreasing number of test components and procedures appears to enhance usability. However, individual test steps still need to be easy to understand and carry out. Mechanisms for providing feedback so the user has the potential to recover from errors can also contribute to a more usable test.[48]

3.3.5 *Training required*
Minimum requirement
User is able to conduct test correctly after brief review of instructions. Support should be available in case of questions.

Optimistic requirement
Conducting the test is self-explanatory and intuitive: no training needed. Support is available in case of questions.

Rationale
The less training and learning that is required of the user to conduct the test correctly, the more likely the success for correct test conduct.

Evidence from literature
Training involves the time during which users can acquaint themselves with device operation and the training materials.[62] A study in Singapore showed that, although users found the test easy to use and instructions easy to understand, 85% still failed to perform all steps correctly, and 56% had an invalid result because of incorrect test performance. This suggests errors are likely even when steps appear simple to the user.[66] Stakeholders desire minimal training required (even for health care providers conducting the test). Hence, learning time to conduct the test should be minimal. Support for testing should be available as needed.[69] Correct use of an RDT significantly increases by adding a simplified job aid beyond instructions only, and correct use increases even more with training.[63]

Evidence from PATH studies

Study participants suggest that lay users should be able to conduct the test with little room for user error by following the provided instructions.[9] One user said, "The pictures should show you clearly what to do." This makes the case for simple and intuitive test design with little or no additional training aside from instructions.[48] However, few of the tests were conducted without an error or problem of some sort. Upon questioning, the majority of respondents agreed or strongly agreed that they found the test easy to do or felt confident conducting the test. Almost all South African respondents said they would use the self-tests themselves; however, in interviews they provided caveats for future self-test use, including need for better instructions or expert guidance such as training before testing.[48] Other mechanisms for instructing naïve users how to conduct the test should be considered. For example, community education sessions to demonstrate the test steps before distributing the tests were employed by Choko et al in Malawi. Alternative training options that can supplement, confirm the instructions, or provide additional support could be helpful and can be explored.[48]

3.4   Operational requirements

3.4.1   Operating conditions
Minimum requirement

Operation between 15°C and 40°C at an altitude up to 2,000 meters, extremely low relative humidity to condensing humidity, and result interpretation in average-light settings.

Optimistic requirement

Operation between 10°C and 45°C at an altitude up to 3,000 meters, extremely low relative humidity to condensing humidity, and result interpretation in low-light settings.

Rationale

The HIV self-test will have utility in a large number of settings with varying environmental conditions. The test must be functional in high and low temperatures and humidity and a range of altitudes. It is unreasonable to expect non-instrumented tests involving fluid components to function below freezing.

Evidence from literature

The test will be used by consumers in many different settings and locations. The test must be able to perform accurately in all of those conditions.[70-72] Other extreme (below freezing) temperatures should also not be forgotten.[45]

Evidence from PATH studies

Laboratory data generated by evaluating rapid tests at various operating conditions indicated that tests without membrane covers/labels are vulnerable to poor performance when run at low relative humidity (<15%), especially at elevated temperatures. This is presumably due to fluid evaporation from the membrane and not allowing the test to run to completion.

Other

While not validated, other areas of concern are signal stability at elevated humidity, especially in a device format where intended directional fluid flow could be reversed (backflow) as the device achieves equilibrium.

3.4.2   Sample types
Minimum requirement

Oral fluid/saliva or finger-prick whole blood.

Optimistic requirement
Oral fluid/saliva, finger-prick whole blood, not to exclude the possibility of other fluids (e.g., urine) if data support the use of the sample.

Rationale
Choice and convenience of sample are important for acceptance and uptake of self-testing. Oral fluid is seen as a less invasive sample type, and at least one oral fluid HIV rapid test exists. Finger-prick whole blood most closely represents the sample used for confirmatory testing and some believe offers the best sensitivity.

Evidence from literature
Oral fluid testing has the potential advantage over blood-based tests due to convenience, noninvasiveness, and ease of specimen collection. However, while oral fluid tests are generally accurate, their positive predictive value in low-prevalence settings is less than blood-based tests, and they are less sensitive in detecting acute infection but considered sufficiently accurate for use in self-testing programs. Although not yet extensively evaluated in field settings, oral fluid kits for self-testing have been found to be acceptable. Evaluation of accuracy, use, linkage to care, and behavioral outcomes are priority questions.[20] The pooled sensitivity of the test in oral specimens was lower than the test's sensitivity in finger-stick specimens, a difference of about 2%. However, the specificity estimates were similar for both specimens. The lower sensitivity of the test in oral mucosal transudate compared with blood specimens is probably because of a lower quantity of HIV antibodies in oral mucosal transudate than in whole blood. The titer of HIV antibodies is also low in acute HIV infection before seroconversion, hence the increased possibility that oral testing might miss more acute HIV infections than tests with blood specimens because of its lower sensitivity.[30]

Evidence from PATH studies
PATH studies verified the literature findings and found at least one suggestion of alternate body fluids as well. Needle phobia and disposal of used sharps may also be important points for considering sample types. Ease of sample collection proved problematic for both oral swab and finger-prick whole blood (in particular lancet use), and improvements in sample collection technology could influence sample type selection. Concerns about the messaging of testing for HIV in oral fluid versus the ability to contract HIV from oral fluid were raised.

3.4.3   Method of sample collection
Minimum requirement
Blood-based samples—finger-prick with lancet; oral fluid-based samples—swab or spit.

Optimistic requirement
Blood-based samples—simple, easy-to-use transdermal collection; oral fluid-based samples—swab.

Rationale
Lancets, especially safety lancets, are difficult for untrained individuals to use. Safe and comfortable options for self-testers are important.

Evidence from literature
This seemingly commonplace procedure may present a significant barrier for patients who are challenged with needle phobia. It is estimated that approximately 10% of patients (children and adults) are "needlephobic."[73] Most participants had never taken a finger-prick blood sample before the study and had some difficulty with their initial attempts. The most commonly observed problem was inadequate puncturing technique.[63]

Evidence from PATH studies
Some needle-phobic individuals were observed, but this prevented only a few from collecting a sample. Difficulties with available collection methods indicated improvements in this area could greatly improve properly conducting the procedure. From a table depicting user failure modes (section 3.2.8), successful sample collection ranged from 30% to 65% across the five prototypes tested. Multiple participants used more than one safety lancet, indicating difficulty using them and a learning curve, which does not support integrating a lancet into the device. Also, generic (non-safety lancets) or personal objects were used in the study to obtain a blood sample because several participants found them easier to understand and use. The use of non-safety lancets potentially introduces unsafe practices for the self-tester and waste disposal issues.

3.4.4   Sample volume
Minimum requirement
Finger-prick capillary blood (maximum 50 μL); multiple gum swabs or prolonged oral fluid collection (up to one minute).

Optimistic requirement
Finger-prick capillary blood (maximum 10 μL); one swab of gums for oral fluid.

Rationale
Current RDT sample volume for testing varies from 5 μL to 60 μL, depending on test type and manufacturer. Precision of sample volume can be important. Tests utilizing oral fluid require more specifics on the method of collection than on precise sample volume (e.g., one swab of the gums).

Evidence from literature
Smaller volumes required would minimize the need for multiple pricks due to insufficient draw volumes. Furthermore, finger pricking can be highly variable depending on the skill of the tester, leading to volume variability (PATH internal data). While this study did not directly measure the blood volume transferred, qualitative assessment suggests that testers in all groups sometimes obtained too little or too much blood.[63] High variability in the amount of blood transferred is cause for concern: inadequate volume can reduce sensitivity while excess volume may cause background staining and obscure faint results (PATH internal data). Manufacturers should work to improve the design of blood collection devices to reduce the risk of error.[63] Studies related to lancets used for blood sugar testing in diabetics indicate variable performance in extracting proper amount of blood for a high percentage of testers.[74,75]

Evidence from PATH studies
The oral fluid sample collection method did not measure volume, but the PATH study did look at how the swab was collected. Methodology was poor, possibly indicating the need for better instructions or a more intuitive method of sample collection. Participants were seen collecting samples from teeth and tongues. Catastrophic oral fluid sample collection (using the wrong end of the swab, putting other liquid on the swab before sample collection) was observed. Finger-prick whole blood sample collection was also problematic. This included problems with lancet use, pipette use, and measuring the sample volume. Smaller sample volumes generally were collected with fewer problems. This could be because of training (again, possibly illustrating the need for better instructions) or that blood collection and transfer devices are designed for professional use, not self-testing. Improvements in sample volume (which has implications with test sensitivity) could benefit new tests (similar to blood glucose testing). It has also been noted from laboratory experiments that certain tests perform better with increased sample volume, while others perform better with decreased sample volume. Therefore, it is important for the test to accurately and reliably deliver the tolerable sample volume and provide quality feedback to the tester.

Also, if a saliva sample is collected by spitting, sample volume could likely become an issue. However, it is reasonable to believe that most individuals could collect approximately 1 mL of saliva in a reasonable amount of time.

3.4.5   Sample dilution/manipulation
Minimum requirement
Minimal sample processing, no more than one operator step; diluent supplied with kit.

Optimistic requirement
No sample dilution/manipulation or integrated sample dilution/manipulation.

Rationale
In general, fewer steps in handling would result in decreased chances for operator-induced error. In low-resource settings, clean water is scarce.

Evidence from literature
Additional steps and manipulation (e.g., sample to capillary tubes and buffer addition) increase potential areas for error.[54]

Evidence from PATH studies
Sample processing (including measuring and transferring liquids) proved to be difficult for some participants. Eliminating or automating this step could improve usability. From a table summarizing user induced failure modes (section 3.2.8), successful sample transfer ranged from 35% to 59% across three prototypes tested.

3.4.6   Need for a follow-up test
Minimum requirement
If positive, referral to a health care provider is required.

Optimistic requirement
If positive, referral to a health care provider is required.

Rationale
Linkage to care after a positive test result is important. An HIV self-test must be seen as a screening test to triage those who need follow-up care.

Evidence from literature
In total, 44 patients were identified as false positives in HIV programs in the Democratic Republic of Congo, two in Burundi, and seven in Ethiopia. Despite potential damage to program reputations, no impact in terms of testing uptake occurred, with mean monthly testing volumes stable after the introduction of retesting. In order to prevent the problem, training, supervision, and QC of testing procedures were strengthened. A simple and feasible confirmation test was added to the test algorithm.[76] WHO and most regulatory bodies (FDA, ministries of health, etc.) recommend follow-up testing. New guidelines of where self-testers should enter into the testing algorithm are in discussion. In high-resource settings, the predominant thought is to have the individual enter the algorithm from the beginning.

Evidence from PATH studies
PATH data support the literature findings that follow-up testing of positive results is important to both self-testers as well as key stakeholders. Messaging for follow-up of negative results is less clear and may need context-specific messaging about retesting intervals based on risk factors.

3.4.7   Time to result
Minimum requirement
Twenty minutes or less.

Optimistic requirement
Five minutes or less.

Rationale
Shorter test turnaround time leads to overall improvement in user acceptance, decreased anxieties, higher throughput, decreased workload, and decreased systematic error.

Evidence from literature
Product inserts for currently available rapid tests and self-tests provide results in 20 minutes and are acceptable to some (e.g., OraQuick® insert).[77] Literature also shows that some testers prefer more rapid results.[52]

Evidence from PATH studies
Most participants did not wait the time indicated in the instructions, most likely due to the fact that they knew they were using non-functional tests that did not yield results (participants were informed of this prior to participating in the study). Some participants spent significant amounts of time in the study room, some even repeating the procedure, including wait times. We are unable to extrapolate how this translates to self-testing in the setting of the tester's choice. Some participants that conducted tests with "instant" results waited a period of time for their results, indicating either that it may not have been clear when to read the results or a bias from their expectations of wait time required for other testing they may have been exposed to.

3.4.8   Duration of valid sample (time from taking sample to insertion in device)
Minimum requirement
Immediate use of sample.

Optimistic requirement
Sample valid for greater than one hour (then result gives "invalid" rather than "false").

Rationale
Most self-testers will introduce their sample into the test and complete the test immediately, as designed. However, it is reasonable to expect that individuals may encounter circumstances where they collect a sample and are interrupted before they can complete the test.

Evidence from literature
Literature on the duration of sample validity for self-testing does not appear to exist.

Evidence from PATH studies
Laboratory data indicates that some currently available tests can give correct results with contrived and serum/plasma samples that have been archived for long periods of time, and that samples can stay at ambient temperature for at least one hour prior to use. However, this is likely very sample-, test-, and operational environment-specific. The formulation of most test control features is not intended for this purpose. Adaptation of test controls for sample quality could be advantageous.

3.4.9   Duration of valid result
Minimum requirement
Results valid to be read for up to one hour after performing the test. Results are stable (do not convert from negative to positive) during this time period.

Optimistic requirement
Results valid to be read for 24 hours or longer after performing the test. Results are stable and do not change. Another optimistic option is results are "masked" or destroyed after a specified read time period to ensure privacy.

Rationale
Reading test result before or after the reading window stated by the manufacturer may yield erroneous results. Extending the period that the test results are stable and can be read could be important for individuals who are interrupted during their testing procedure, those who do not test in adequate lighting to accurately interpret results (and interpret them a second time under different conditions), the worried tester who fails to discard the test when appropriate and continues to monitor the test result, and those testers who wish to share their results with others (e.g., partner, family, provider).

Evidence from literature
As a key consideration of self-testing is access to counseling and referral to prevention, care, and treatment services, stakeholders have mentioned that it would be ideal for users to be able to show their result to a health care provider when they seek services after the test is complete. Therefore, the result must remain constant and not change over a specific period of time.[50]

Evidence from PATH studies
Laboratory data suggest that the stability of results is test-specific and possibly sample-specific (e.g., some samples tend to give false positives over time and extremely low positives such as those from early seroconverters). Depending on the test, we have repeatedly observed discordant samples during the manufacturer's recommended read window (a test that indicates the result can be read between 10 and 20 minutes may give a negative result at 10 minutes and a positive result at 20 minutes).

Other concerns with HIV self-testing include privacy and coercion.[9] Results that are masked or destroyed could mitigate these issues.

3.4.10   Assay control
Minimum requirement
Procedural control internalized in the cartridge for each individual test.

Optimistic requirement
Control internalized in the cartridge for each individual test (indicating sample adequacy and that the assay was performed correctly).

Rationale
Controls included in tests can be procedural, indicating that the test has been run, or functional, indicating that the test procedure was followed correctly. The former is useful in informing the user that the test has been used, but the latter is useful in providing quality feedback to the user, presumably increasing confidence in the results.

Evidence from literature
Literature on the attributes of assay controls does not appear to exist.

Evidence from PATH studies
We have observed that tests with controls that appear only with sample addition are not necessarily indicative of an adequate sample. For instance, a test with a functional control that requires 20 μL of sample may still give a positive control when only 10 μL of sample is delivered. The same test has been shown not to give accurate results with low positives at lower sample volumes.

3.4.11   Device control
Minimum requirement
Indicator of instability or expiration.

Optimistic requirement
Indicator of instability, expiration, inadequate sample, and incorrect procedure or use.

Rationale
A control indicating that the assay is of high quality and appropriate for use should be incorporated in the device and be apparent to the user to indicate quality.

Evidence from literature
Literature on the attributes of assay controls does not appear to exist.

Evidence from PATH studies
Tests that are past their expiration and may give erroneous results retain the ability to show a positive control. Manufacturers typically label devices with expiration dates, but these are often cryptic or obscure, and it is not included in the instructions to check the expiration date before proceeding.

3.5   Kit requirements

3.5.1   Unit packaging
Minimum Requirement
All materials and reagents, including buffers or other consumables, required for testing one self-test user with the assay should be included in an individually packaged, self-contained kit.

Optimistic requirement
A complete, self-contained kit for testing only one self-test user with further simplification by maximizing component integration as much as possible would be useful.

Rationale
From literature and field work, packaging must be as small (discreet) and as complete as possible.

Evidence from literature
All components should be included in the individual test package or box of tests.[78] This should preferably include QC reagents and appropriate, single-use lancets for finger-pick blood collection as required.[45,50,79]

Evidence from PATH studies
All field sites frequently echoed the need for complete packaging of all components and yet minimizing the number of components as much as possible to avoid confusion in component identification.[11]

3.5.2   Unit labelling
Minimum requirement
Generic multi-lingual packaging, increased use of symbolic representation versus text, adherence to WHO/GHTF RDT-specific guidelines.

Optimistic requirement
Context-specific, culturally relevant/acceptable packaging. Further refinement, consolidation, and enforcement of WHO/GHTF guidelines.[80]

Rationale
Self-test end users in low-resource countries represent a varied educational background, but predominantly have little to no education. The challenge to clearly communicate how to use the test is best done by highly simplified labeling that is intuitively conveyed and pictorial. Furthermore, labels must include a complete list of QA specifications, particularly expiration date.

Evidence from literature
Readability, accuracy, successful product packaging, design, and labeling remain a problem, directly affecting correct use of kits. Such problems include:
  1. Issues with desiccants.
  2. Insufficient space for sample identification on cassettes.
  3. Ambiguous demarcation of sample wells.
  4. Readability of inserts greater than sixth-grade level.
  5. Design issues leading to gross errors (e.g., a writing surface only amenable to a felt-tip pen).
  6. Quality of packaging.[59,81,82]

Parekh et al also points out deficiencies in product labeling—the lack of test kit names, lot numbers, and expiration dates—makes it impossible to identify or troubleshoot problems.[38]

Evidence from PATH studies
Opinions were gathered from key stakeholders and lay users regarding package labeling and test labeling, some of which reinforce what is currently highlighted in literature. Other comments raise new specific concerns relevant to sub-Saharan African locations. In regards to package labeling, clear instructions for how to open the package must be intuitive. A common problem was that lay users had difficulty opening test packages. In some cases, participants resorted to using other alternatives like their teeth or whatever was within reach (such as the pencil that was provided) in an attempt to open it. Other notable information was that black and white colors should be avoided since some Africans and natives consider these colors to be associated with witchcraft,[11] and the package labeling be positively branded, avoiding words that may carry negative stigma:

> *"It's like people don't go and ask for condoms people ask for Trust. Give me Trust, give me Durex, not give me condoms... People shouldn't be shy. Before that, people used to be shy to ask for condoms but now… normalize the brand so that it is okay to go and ask for Trust, it's okay to go and ask for OraQuick."*[11]

Linkage to care was another suggestion to package labeling:

> *"The test kit package should have a list of health facilities or organizations of where to seek help after testing, where the counselling centers. These can also include the contacts of where to get a counsellor if one needs further help after testing."*[11]

In regards to test labeling, a common problem was the lack of adequate labeling of locations of test lines and test components. For one prototype, the lack of location of test lines directly contributed to significant result misinterpretation. Since the test did not explicitly label the locations of the test and control lines on the cassette, prototype FS2, this test had the lowest frequency of correctly interpreted negative results (48.3%) and invalid results without a control line (41.4%). The highest percentage of participants (90.8%) correctly identified the results of the flow-through test, which utilized different symbols for control and test line.[49] Another test labeling recommendation was that test components should be numbered and the numbering should be matched to test instructions.[49] Lastly, appropriate warnings should be placed on liquid components (e.g., buffer) to dissuade misappropriate use.[11]

3.5.3   Unit size
Minimum requirement
100 kits/six cubic feet (to be re-evaluated).

Optimistic requirement
150 kits/six cubic feet (to be re-evaluated).

Rationale
Test size must be as small as possible to fit the smallest test packaging size possible. A common opinion shared by test subjects is the need for discretion during purchasing. A decrease in the size of the kit unit results in more efficient storage and transport advantages as well as possible cost benefits.

Evidence from literature
Information on test size was not found in literature. The minimal and optimistic requirements are based on the dimensional sizes of HIV RDT kits used in PATH's stability and guard banding study. We note that package sizes could be significantly reduced from their current size.

Evidence from PATH studies
Both key stakeholders and lay users frequently urged that the test should be small enough to fit in a pocket.[9] The emphasis on decreasing the size of the test package as much as possible was for reasons of portability and discretion.

> *"I think it should be small enough for someone to actually put in their pocket, you don't want a bulky thing that someone you know will buy from the supermarket and everyone is seeing what I am carrying."*[9]

3.5.4   Kit stability (shelf life) and storage conditions
Minimum requirement
Stable for 12 months at 2°C to 40°C, 70% humidity, including transport stress (48 hours with fluctuations up to 50°C and down to 0°C).

Optimistic requirement
Stable for 24 months at 0°C to 45°C, 90% humidity, including transport stress (48 hours with fluctuations up to 50°C and down to 0°C).

Rationale
Self-tests are transported to distribution centers (such as pharmacies) and eventually to consumers through a variety of supply chain routes/mechanisms. In low-resource settings, supply chain systems are convoluted systems and may cause significant delays in getting a test to the end user. Self-tests must be hardy against long delays and environmental conditions in order to have as long of a shelf life as possible.

Evidence from literature

Exposure to extreme temperatures is a major contributor to poor performance of RDTs, particularly during transfer from the manufacturer, and transport within a country as well as storage. High humidity can rapidly degrade RDTs, especially prolonged exposure to humidity after removal from the envelope or if the envelope is damaged.[71,83] A number of studies underscore the frequent occurrence of temperatures above 30°C in low-resource settings.[58,70,72,84] Anderson et al recommend that tests should have an extended shelf life (>6 months and preferably >12 months) at ambient conditions. Temperatures may commonly exceed 40°C in many countries with high HIV prevalence, often with high humidity.[45] Temperatures at the other extreme (below freezing) should also not be forgotten.[45] Pant Pai et al noted a drop in test performance with kits nearing their expiration date (<1 month) and that this could be avoided by extending their viability period. To sum up, these facts need to be emphasized in countries with less stringent QC measures and where devices are used beyond their expiration dates.[30] Lastly, Usdin et al emphasized that the lack of timely shipment of tests to clinics in low-resource settings results in low supply or expired products.[50] Therefore, we can assume that maximization of shelf life could result in greater product viability.[50]

Evidence from PATH studies

A PATH temperature stability study (prepared for publication) and other literature demonstrate a high frequency for temperatures to exceed 30°C. Therefore, it may not be acceptable for an upper temperature limit for test storage to be 30°C for tests intended for use in some low-resource settings.[72] A new minimum that should be considered is 40°C for 12 months with an optimal stability requirement with an upper limit of 40°C for 24 months. Information gathered from the field work corroborates this need to increase tolerance to higher temperatures and extending stability as long as possible, with a common agreement of a minimum shelf life of one year.[11]

> *"…As a person who wants the self-testing I just go and get the kit, see that it is having the shelf life you see now it has not expired. But for somebody who is procuring I would like to have something which is having a long shelf life so that I can keep it, I don't lose it because it will expire in my shelf and so on. But for the country, of course, I have not seen a rapid test kit which has got more than 24 months of shelf life. Actually Determine has got 12, Unigold I think has got 18… months or something. So this will depend on the manufacturer and the stability of the antigen on the kit and whatever but if we can have a shelf life of ten years I tell you let us have a shelf life of ten years but I don't know whether there are. (Procure001)"[11]*

From the key stakeholder interviews and usability study, test stability must be maximized:

> *"For the shelf life one it has to be a dry package, should not need some refrigeration, should be at room temperature with a minimum of at least the current practice of like the test is between six to one year two years."[11]*

3.5.5   Cold chain

Minimum requirement

None required at any point in supply chain or storage.

Optimistic requirement

None required at any point in supply chain or storage.

Rationale
The requirement for a cold chain must be eliminated due to lack of consistent cold chain infrastructure and the diverse nature of self-test distribution systems.

Evidence from literature
Intermittent availability of electricity and lack of refrigeration make testing increasingly more difficult as one approaches primary levels of health care or in poorer countries, obviating the need for cold chain. Kits that need storage at 4°C to 8°C should be avoided unless there is a good refrigeration facility and constant power supply.[56,58,85] Most HIV rapid tests are simple to perform and do not require cold chain for transportation and storage, making them suitable for non-laboratory settings and to meet the demands of large testing volume. For example, there are several thousand lay persons performing rapid tests in more than 5,500 sites in Kenya.[38]

Kits that need storage at 4°C to 8°C should be avoided unless there is a good refrigeration facility and constant power supply.[38]

Evidence from PATH studies
The self-test kit must not require cold chain. A cold chain requirement would otherwise severely limit placement:

> *"...Most of the test kits are stored in fridges. This test if it can be stored at room temperature, we can have them in the toilets attached to the bars, offices, large organizations... where we just put those test kits and people can pick them when they are not being seen by others. (Acad002)"*[11]

3.5.6   Clean water
Minimum requirement
No water required.

Optimistic requirement
No water required.

Rationale
The requirement for clean water must be eliminated to due to lack of consistent access to clean water in low-resource countries.

Evidence from literature
Consistent availability of clean water is variable at best. Water shortages and contamination of water sources are commonplace.[56,86] Running water and electricity may or may not be available, and power is at best intermittent with wide fluctuations in voltage. The ambient temperature may range from 10°C to more than 40°C.[58]

Evidence from PATH studies
No further evidence.

3.5.7   Electrical power
Minimum
No electrical power required.

Optimistic
No electrical power required.

Rationale
No further evidence.

Evidence from literature
Many settings where self-testing is appropriate either lack access to electricity entirely or have only intermittent electricity. The most effective point-of-care rapid tests must not rely on a power source.[58,87]

3.5.8   Instrumentation/additional third-party consumables
Minimum requirement
None. Disposable test only.

Optimistic requirement
None. Disposable test only.

Rationale
A self-test diagnostic must remain as consumer-oriented as possible. Therefore, no additional instrumentation or third-party consumables must be required.

Evidence from literature
The use of a reader or other equipment would add unreasonable expense and complexity to the test. Pricing should be comparable to non-reader-based tests, and complexity should be minimized.[45]

Evidence from PATH studies
Recommendations were made that a self-test kit should include an extra kit for confirmatory testing. PATH argues that this would contradict simplification of the test as well as complicate other TPP parameters (e.g., decrease ease of use).

3.5.9   Other supplies
Minimum requirement
No supplies other than the bare minimum to perform the test.

Optimistic requirement
No supplies other than the bare minimum to perform the test.

Rationale
A self-test diagnostic must remain as consumer-oriented as possible; no additional supplies must be required.

Evidence from literature
Tests must be simple to perform and to interpret, by personnel with no/minimal scientific training, with all components included in the individual test package or box of tests. This should preferably include QC reagents and appropriate, single-use lancets for finger-prick
blood collection where required.[45]

Evidence from PATH studies
Two recommendations were put forth as additional equipment for a self-test: safety gloves and additional lancets. We reasonably conclude, however, that the bare minimal components be supplied in the test kit.

3.5.10   Safety precautions (biosafety requirements)
Minimum requirement
Closed, self-contained system; unprocessed sample transfer only, no open handling of biohazardous material. Biohazard information should be clearly mentioned in instructions.

Optimal requirement
Closed, self-contained system; integrated sample transfer, no biohazard risk to user or others.

Rationale
A self-test diagnostic must remain as consumer-oriented as possible; therefore, no biohazardous chemicals must be used.

Evidence from literature
To ensure the safety of a finger-prick rapid test, a single-use disposable lancet would need to be developed and tested. WHO guidelines recommend both single use and retractable lancets.[88] Self-collected finger-prick specimens have been collected historically for diabetes testing without serious negative consequences. Alternatively, a rapid oral fluid test could be developed and tested that may have fewer biohazard risks.[4,59]

Evidence from PATH studies
The field work elicited concerns about the biohazardous potential of blood, particularly in regards to proper disposal of a used self-test. One commentator did recommend that gloves be placed in the test kit.

3.5.11   Waste management
Minimum requirement
Disposal of cartridge in routine waste stream; no need for sharps or biohazardous waste handling.

Optimistic requirement
Disposal in routine waste stream; compostable materials as applicable (packaging, etc.).

Rationale
Inadequate and insufficient waste disposal systems are prevalent in low-resource settings. Therefore, waste must be minimized.

Evidence from literature
Waste disposal is a problem in low-resource countries, with most nations practicing open dumping for waste disposal.[89] Insufficient waste management infrastructure is found in rapidly growing urban areas and in rural areas.[58,89] Minimal generation of contaminated waste[45] should be an influential factor in choosing a test for country use as there is the increasing concern about the environmental disposal of chemical and biological waste.[38,57,58] Mavedzenge et al pointed out one advantage of oral fluid testing: disposal of biohazardous material is an important safety concern, with oral fluid tests having significantly less biohazard risk than other tests. Improper disposal of used sharps is likely to be of greater concern when test kits are used informally than when used in a formal self-testing system. Oral fluid tests are easy to use, do not involve sharps disposal, and have low technical demands for specimen collection, which make these potentially attractive choices.[25] Desirable features include low cost and minimal generation of contaminated waste. The availability of QA standards for field use is highly desirable and is required for product registration in many countries.[45]

Evidence from PATH studies
A need for proper disposal of used tests was a common sentiment in the field studies. Solutions, however, were lacking among the respondents. The majority of lay users mentioned toilets and dust bins as the likely places for disposal of self-tests.[65]

As captured by the inter-country report, self-testing in a home environment creates a problem of waste disposal that did not exist with facility-based testing. Respondents felt that guidance on how to dispose of the kits safely was an important issue and that information on this should be provided, particularly for tests using blood samples. One respondent suggested that kits using blood samples were not appropriate at all due to the problem of safe disposal.[9]

3.5.12   Kit quality indicators
Minimum requirement
Clear, explicit marking with expiration date.

Optimistic requirement
Clear indicators of a "bad" test (i.e., exposed to conditions that could compromise test performance, such as age of test, temperature, humidity, or physical damage).

Rationale
Consumers should have indicators of quality that are visible to them prior to purchasing and/or using the test to increase the likelihood of using devices that will give a proper result, which will help improve consumer confidence.[80]

Evidence from literature
FDA/CE Mark/GHTF requirements for labeling.

Evidence from PATH studies
According to one comment, the consumer does check the expiration date before purchase. On the basis of field work data and conclusions, symbolic indicators of temperature stability, length of shelf life, and a statement that no requirements are needed for electricity, water, and cold storage should also be included on product packaging. During a technical advisory group meeting on January 28, 2012, the idea of a mechanism to disallow further result interpretation after the test window of evaluation was promoted by two experts in the field.[50]

3.6   Commercialization requirements

3.6.1   Product registration, WHO prequalification, regulatory approval
Minimum requirement
Manufactured to cGMP standards and specific requirements necessary for legal sale and use in each target country.

Optimistic requirement
Manufactured pursuant to cGMP; ISO 13485-certified and authorized for use by a credible regulatory authority (EU, FDA) and/or WHO prequalified and registered for *in vitro* diagnostic use and/or CLIA waived.

Rationale
The absolute minimum requirement is the authority to sell/distribute in the target countries; cGMP guidelines are the industry standard. Optimistic requirements include a waiver, prequalification, and/or

approval from a globally recognized regulatory authority. However, the specific regulatory approvals may differ from country to country.

Evidence from literature
It is useful to note that there are two criteria to consider for regulatory purposes. The first is the legal authority to sell the product; the second is the assurance of delivering a safe, effective, and high-quality product. These are not necessarily mutually inclusive.

- ISO 13485 is the international standard related to quality management systems for the design and manufacture of medical devices.[90]
- The CLIA waiver is an FDA certification that designates a device as simple, accurate, and safe enough to warrant waiver of regulatory oversight.[58,91] Most HIV rapid tests that use finger-prick blood or saliva at the point of care are CLIA waived.[85] All tests approved for home use are automatically CLIA waived.
- The CE Mark is a mandatory conformity mark for products sold in the European Economic Area.[90]
- OraQuick ADVANCE® HIV-1/2 is FDA approved for oral fluid testing of HIV in a professional setting.[92] The OraQuick® In-Home Oral HIV Test was approved by the FDA on July 3, 2012.[92]
- Regulatory approval requirements vary between countries.[58,91]

The availability of QA standards for field use is highly desirable, and is required for product registration in many countries.[45]

Evidence from PATH studies
Primary data consisted of a description of what study informants believe will or should be required of an HIV self-test from a regulatory perspective. Key informants are not necessarily country-level regulatory experts. In general, the sentiment from Kenya informants is that WHO guidelines (regulatory and otherwise) will be useful, but not sufficient, for implementation.[11] Mechanisms for QA were specifically noted as important to implementation.[11]

In Malawi:

> *"In line with WHO guidance, some of the participants expressed that they are willing to implement HIV self-test as long as the test kits are approved by the World Health Organization and that the self-testing services adheres to WHO key components on HIV testing services such as counseling, linkage to care."*[23]

3.6.2   Target cost per result/end user
Minimum requirement
Fully subsidized for poor target populations through public clinics. Price to affluent target populations or through private distribution is country-specific. South Africa: R20–R40 (~US$2–US$4). Kenya: KES 300 (~US$3) Malawi: MK 1000 (~US$2.50); for a non-country-specific estimate, ~US$1.06 per test.

Optimistic requirement
Fully subsidized for poor target populations through public clinics. Price to affluent target populations or through private distribution is country-specific. South Africa: R10 (~US$1). Kenya: KES 30–KES 50 (~US$0.30–US$0.50). Malawi: MWK 100 (~US$0.25); for a non-country-specific estimate, ~US$0.72.

Rationale

It is presumed that the target cost should align with the willingness of the test purchasers to pay. In some scenarios, this is the end user, but where tests are freely distributed the purchaser is typically a government or global health organization. Ranges of willingness to pay describe the minimum and optimistic requirements. Please also note that this data uses a relatively small data set, and that no information from official government sources was obtained regarding their willingness to subsidize the cost of tests. Willingness to pay is certain to vary between countries, and is therefore described here in that context.

Evidence from literature

According to the Global Fund to Fight AIDS, Tuberculosis and Malaria (referred to here as the Global Fund) procurement data for provider-assisted HIV RDTs from January 2010 to February 2012, the average price paid per test was US$1.06, ranging from US$0.30 to US$4.50 depending on the specific test sold and scale of tender. The self-tests should be, at a minimum, competitive with those tests, with a target end-user price of no more than US$1.06, and an optimal end-user price of ~US$0.72 (the lowest recorded tender for the highest-volume test sold, Determine® HIV-1/2 (Global Fund Procurement Database [PQR], 2010–2012). Health care workers in Kenya were unwilling to pay; they expect the government to pay since HIV is perceived to be an occupational risk.[93] However, this does not necessarily impact the end-user price; it transfers the willingness-to-pay decision from the health care workers to the health ministry.

Also important, but largely beyond the influence of the product design, is the overall "cost to serve." The cost to serve is dictated by the robustness of the logistics infrastructure, training and support costs, and other factors associated with test delivery. The cost to serve can account for up to 30% of the overall cost of instrument-based diagnostic technologies.[53]

Current costs of provider-assisted RDTs may hamper access to over-the-counter tests, and mechanisms to improve global access should be explored.[20]

Evidence from PATH studies

In South Africa, it was noted repeatedly that the willingness to pay on the part of the end user would be highly dependent on the distribution point and the target market. With regards to whether the HIV self-test kits should be sold or distributed for free, participants highlighted that the middle class would most likely prefer buying the HIV self-testing kits in pharmacies and take them home to test, while the poor would need to get the free HIV self-testing kits from government health care facilities and take home to test themselves.[94] Several participants offered their views on pricing for self-tests. In South Africa:

> *"We did the pricing based on Oral Sure, the oral swab, and fairly simple packaging. Much simpler than the way in which the product is sold in the US. We came up with about R100 price to consumer."* (KI: NGO representative 4)[94]

> *"People will happily pay R50 not to have to go and sit in a queue all day to get their HIV status."* (KI: Academic 2)[94]

Another Kenyan informant stated that the HIV self-test should not be more than R10 if sold in pharmacies.[94] Many South African informants said that the HIV self-test should be freely distributed by the government.

> *"Government should pay! Government already provides condoms, tests are essentially free but it depends on how much the test will cost as well. So if you using a self-test, let it*

not cost more than what the government is currently paying right now for HIV tests. (KI: Academic 1)"[94]

Key points from informants in Kenya:
Acceptable cost to the end user will depend on the target market. Generally, informants commented that the tests should be of no cost to the target user and entirely subsidized by the health system. Provider-assisted testing is free in many places, and even a nominal cost is difficult for lower-income populations. Higher-income populations may be willing to pay a low cost (similar to a pregnancy test, KES 50 to KES 300) to avoid having to go to a clinic to obtain the test. Many noted that, even if subsidized, some costs will be incurred if the products are distributed through a pharmacy or other commercial entity. It was also considered to benchmark against the cost of condoms (KES 30 to KES 300).[11]

Key points from informants in Malawi:
Generally, all informant groups, including policy and government officials, felt that tests should be provided free to the end users, particularly poor populations. The presumption is that it would be procured through the National AIDS Commission.

> *"Participants observed that in Malawi there is a policy provision for HIV testing as a free public service coordinated through the government. If self-testing was to be implemented then it has to follow the same policy."*[23]

Expanding beyond public clinics may require a fee for the end-user, however, and if this is the case, it was suggested that the price (possibly a subsidized price) be kept very low, MK 200 to MK 1000 (~US$0.50 to US$2.50)[23] We found no information on what prices the government might be able to bear, but it was suggested that external help might be needed (Global Fund, NGOs).[23] Similar responses were obtained from lay users.

In South Africa, while nearly all respondents said they would use the test if it were free, a very high percentage would also purchase the test themselves if needed. The median price suggested in terms of willingness to pay was R20 to R40 (~US$2 to US$4).[49]

In Kenya, most respondents would be willing to pay for the test, with prices ranging from KES 50 to KES 500 (~US$0.50 to US$5). However, many also felt that the government should subsidize or give out the tests for free so that everyone could use them. It was noted the perception that the value of the test is comparable to a condom, and that a similar pricing would be acceptable.[65]

In Malawi, there was significant concern that so many poor Malawians who would need the test cannot afford to pay much. Pricing suggestions ranged from MWK 100 to MWK 1,000 (US$0.25 to US$2.50). Comparisons to key essentials were noted for pricing:[64]

> *"Let me give you a vivid example, people in the villages are failing to buy a bag of fertilizer at a subsidized price of five hundred kwacha, so they can't buy this test at more than that amount."*[64]

3.6.3 Channels to market
Minimum requirement
Free or nominally priced through public clinics.

Optimistic requirement
Public clinics and multiple private channels to access all key target populations.

Rationale
From the study data it seems that there are two mechanisms to deliver HIV self-tests to the target populations: through existing health care infrastructure and through private commercial channels. At a minimum, it was determined that distribution through public clinics that already perform HIV testing, distribute condoms, perform educational outreach, and HIV counseling would be required to access the most vulnerable groups. Optimally, there would be private sources that would sell the tests and reach a larger segment of the target groups.

Evidence from PATH studies
It is assumed and supported by informant data that the supply/distribution channels should be designed to maximize access to the test, particularly for key target populations. Across all three countries, it was asserted that one of those key populations would be unable to pay and should have a mechanism to obtain tests for free, presumably through government clinics. However, it was also noted that distribution at private settings, most often pharmacies, would also improve access even with the expectation of cost to the end user. A repeated comparison for both scenarios was to follow the lead of condom distribution, and the informants seemed to think it would be appropriate to find both products in the same settings.

Participants in South Africa spoke of different strategies for distributing and scaling up HIV self-tests, ranging from government health care facilities to private health care facilities, pharmacies, workplaces, and mechanical dispensers. Stakeholders felt that HIV self-tests could be conducted in the home or any place where people were comfortable to test themselves. This could also happen in schools, at NGOs, and mobile clinics, depending on the target group to be reached.[94] An NGO representative highlighted how commercial sex workers could be reached and informed about HIV self-testing:

> *"Through outreach to sex-workers, there are many outreach 'spaces' where sex workers come on a regular basis: bars, clubs. Peer educators go there and can access many people through snowballing. Need to think about how marginalized people access services, as they live on the periphery of formal services. The provider of the test would need to be very informed and sensitized for these groups. (KI: NGO representative 3)".[94]*

With regards to whether the HIV self-test kits should be sold or distributed for free, participants in South Africa highlighted that the middle class would most likely prefer to buy the HIV self-testing kits in pharmacies and take them home to test, while the poor would need to get the free HIV self-testing kits from government health care facilities and take them home to test themselves. Several participants offered their views on pricing for self-tests: "People will happily pay R50 not to have to go and sit in a queue all day to get their HIV status" (KI: Academic 2).[94]

In Kenya, distribution channels will depend on the target market, as each market segment will have different needs/priorities. The clearest market segment distinction is by economic status. Lower-income populations will need to obtain the tests for free, likely from a clinic or government source, but more affluent end-users may be willing to pay more for the discretion and convenience of obtaining the test from a pharmacy. Many parallels were made to condom distribution channels: free at public clinics, small fee at private pharmacy/store.[11]

A potential solution was proposed to reach lower-income populations without requiring them to go to a clinic by using community-based distributors who go to households and offer the test. This is already done with birth control pills and condoms, and could use the same distribution channels.[11] In Kenya, supermarkets/groceries were suggested as being poor distribution points because of the lack of oversight and test information.[11]

Two main distribution channels were identified in Malawi: existing health facilities/distribution points, or alternative (non-health service) settings. There was a suggestion to work with organizations, such as Population Services International (PSI), that already distribute products to many of the same target populations. These organizations may be useful advisors or co-distributors.[23] Naïve users in South Africa suggested that the self-test be available the same places where condoms are—clinics, pharmacies, and supermarkets— specifically places where everyone goes for normal daily items to mitigate stigma. There is a belief that if acquired at public clinics it would be free.[49]

> *"Different options were identified as several places from where to purchase the HIV self-test kits including chemists/pharmacies, hospital/clinic, supermarket and shop among others. For some respondents, the self-test kit should be made available everywhere just like condoms.* (Naïve user in Kenya)"[65]

Naïve users in Malawi indicated that distribution should be dependent on the target population. Free tests subsidized by ministries of health and NGOs would be available through public clinics. Private facilities were preferred by some because of convenience, lack of long wait times, and perception of better supply management, though these sites were expected to charge a fee for the tests.[64]

3.6.4   Supply, service and support mechanism
Minimum requirement
Literature within the test package guiding linkage to care and performance of tests. Involvement in supply chain development.

Optimistic requirement
Training programs for distributors or direct participation by manufacturers in providing testing help and post-test direction (*not* counseling). Support via phone or SMS. Control of supply chain, including post-use disposal planning.

Rationale
Test support centers on how the manufacturer will be involved in the supply and post-sale support of their products. At a minimum, it was determined that passive support through product literature and at least cooperation with supply chain development were required. Optimally, the manufacturer would be more involved in training distributors, counselors, and professionals at the point of sale and would take a more direct role in coordinating phone or SMS support, as well as leading supply chain development. Since the manufacturer likely has the most expertise in use of their product, and may also have experience distributing to multiple low-resource countries, the greater their involvement the better.

Evidence from literature
In Burkina Faso, a program was largely successful despite the challenges of device support in remote settings. While the machine (a CD4 diagnostic device) functioned well in the remote and dusty setting of Ouahigouya, communication with the regional distributor was difficult.[95]
Maintaining and calibrating even moderately complex instruments in low-resource settings is challenging and ideally avoided.[58]

Test introduction and adoption in a sustained manner in a health care system would depend on many factors, including supply chain management, to avoid frequent stock-outs. Hence, when developing tests for rural areas, one also needs to take care of the whole supply chain, as illustrated by the need to maintain a continuous supply of vaccines, drugs, bed nets, etc., to these areas under different programs. For diagnostics, one needs to consider not just the part of the chain covering distribution and storage until

the test is used, but also the disposal of diagnostic kit parts as the infectious nature of this waste will make it potentially hazardous if not disposed of properly.[58]

Evidence from PATH studies
While some concerns and ideas were put forth from naïve users and stakeholders in the countries studied, many of their concerns involved actions on the part of the health care system and implementation, rather than product features or manufacturer responsibilities. The stakeholders interviewed did not appear to have interest/expertise in supply chain issues.

Concerns about how to support the product were noted by several informants in Kenya. This point was a key reason why some prefer distribution in clinics over other channels.[11]

In Malawi, it was suggested that the manufacturer effectively train distributors and counselors before scale-up so that they can support the tests directly. While there were no specific solutions put forth, it was also noted that stock-outs are very common with health care supplies and are a major barrier to access. It is unknown how the self-test manufacturers can help to mitigate these issues.[23] Informants suggested a way to contact help via SMS, either from the health system, distributor, or manufacturer, would be very well used.[49]

Naïve users in Kenya only discussed local sources for support , not from the manufacturer.[65] It was suggested that support within the test kit be in the form of a leaflet explaining not only how to use the test, but why to take the test, and what to do after getting a result (even specifically where to go to for care). If problems arise, they would generally expect to go back to the distribution point for help, so these points would need to have appropriate training and information resources. A 24-hour helpline was also suggested, and that phone number should be included in the test documentation. Therefore, manufacturers would need to, at a minimum, work with the helpline facility or even be involved in it directly.[64]

3.6.5 *Quality control*
Minimum requirement
Key quality systems certifications (ISO 13485) and cGMP practices. Full cooperation with QA efforts.

Optimistic requirement
Quality systems certifications, cGMP practices. Proactive design for non-ideal handling scenarios. Full participation with QA efforts.

Rationale
While there are undeniably quality risks, it is important to distinguish the QC and QA aspects. QC is best controlled at the point of manufacture, and is best regulated by well-established quality certifications (ISO 13485 and cGMP systems). QA is better performed externally by regulatory authorities. In general, the quality standards for self-tests should at least meet those for professional use HIV tests.

Evidence from literature
Due to high product variations in product QA, addressing problems of selecting and quality-controlling RDTs down to the point of care remains one of the main challenges facing their successful use.[96] Tests must undergo and pass verification in the field and laboratory validation studies, and these trials should be independent of the manufacturer.[45] All test kits should be manufactured with the highest standards. Some kits are produced by the same manufacturers but rebranded and sold by different companies, and occasionally the same test kit is manufactured at multiple sites, not all of which follow the same regulatory standards.[38] Quality control of diagnostics products is still highly insufficient. As a result, a large number of cheap diagnostics of questionable quality are sold and used without any evidence of

effectiveness. Companies manufacturing and marketing high-quality tests are unable to compete with cheap, low-quality tests. There is an urgent need for adoption of quality standards in the approval of diagnostic tests.[58]

Evidence from PATH studies
While product quality is clearly of high importance, little discussion of test quality was noted in the study. There are concerns about poor-quality tests, but it is left to the manufacturer to address them. Issues with test validity from handling after they leave the manufacturer's control are an important risk factor, but are best mitigated by the manufacturer by developing a very robust test that requires little or no special handling by the distributor and end user. Some informants in Kenya used QC challenges as a reason to distribute in clinics or other controlled settings.[11] Malawian informants noted concerns about quality of tests during local storage after distribution.[23]

4.0 Change management

Version	Date	Key changes from previous version
1.0	November 2011	Initial draft
2.0	June 2012	Updated TPP based on technical advisory group input
3.0	May 2013	Interim update based on latest knowledge; change format
4.0	January 2014	Update based on latest knowledge; incorporate new literature, results from lab and usability studies; change format
4.1	March 2014	Update based on review

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