Digital Interventions for HIV Self-Testing

The feasibility of HIV self-testing in South Africa
and the introduction of digital interventions
to measure and optimise programmatic impact

Alex Emilio Fischer

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Digitale interventions voor zelftesten op hiv

De haalbaarheid van zelftesten op hiv in Zuid-Afrka en de introductie van digitale interventies om de programmatische impact te meten en optimaliseren

(met een samenvatting in het Nederlands)

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Abbreviations

3tc – Lamivudine
AIDS – Acquired immunodeficiency syndrome
AOR – adjusted odds ratio
App – application
ART – anti-retroviral therapy
ARV – Anti-retroviral drugs
AZT – Zidovudine
CHC – Community health Centre
EIA – enzyme-linked immunosorbent assays
EID – early infant HIV diagnosis
EMP – Department of Essential Medicines and Health Products
EPI – Expanded Programme on Immunization
FDA – Food and Drug Administration
FHIR – Fast Healthcare Interoperability Resources
FS – fingerstick whole-blood
GDPR – General Data Protection Regulation
HAART – highly active antiretroviral therapies
HCW – healthcare workers
HIV – human immunodeficiency virus
HIVST – HIV self-testing
HREC – Human Research Ethics Committee
HSC – home sample collection
HSTAR – HIV Self-Testing Assessments and Research
HTC – HIV testing and counselling
HTLV – T-lymphotrophic virus
HTS – HIV testing services
ICF – informed consent forms
IEC – International Electrotechnical Commission
IFA – immunofluorescence assay
IFU – instructions-for-use
IMDRF – International Medical Device Regulators Forum
IQR – interquartile range
ISO– International Organization for Standardization
IVD – In Vitro Diagnostics
LMIC – low- and middle-income countries
M&E – monitoring and evaluation
mHealth – mobile health
MSM – men who have sex with men
NHLS – National Health Laboratory Service
NRTI – nucleoside reverse transcriptase inhibitors
OF – oral fluid
PEPFAR – President's Emergency Plan for AIDS Relief

PI – protease inhibitors
PIN – personal identification number
PLHIV – people living with HIV
POPI – Protection of Personal Information
PQ – prequalification
PrEP – pre-exposure prophylaxis
PRISM – Program for Readability in Science and Medicine
PWA – Progressive Web App
RCT – randomly controlled trial
RDT – rapid diagnostic tests
SA – South Africa
SAHPRA – South African Health Products Regulatory Authority
SaMD – software as a medical device
SANAS – South African National Accreditation System
SD – standard deviation
SMOG – Simple Measure of Gobbledygook
SMS – short message service
SIV – simian immunodeficiency virus
STI – sexually transmitted infection
TasP – treatment-as-prevention
TB – tuberculosis
U=U – undetectable = untransmittable
UI – usability index
UTT – universal test and treat
VMMC – Voluntary male medical circumcision
WHO – World Health Organization
WHOPQ – WHO prequalification
Wits RHI – Wits Reproductive Health and HIV Institute

Preface

When I first moved to South Africa seven years ago to start my Masters in Public Health, I had big plans. As a young, naive researcher I thought that my dissertation was going to change the world. I was investigating mobile health interventions for diabetes and my plan was to design, build and implement an app that would help thousands of people manage their diabetes, leading to improved glycaemic control. After starting my studies, I soon realised that my plan was impossible to achieve as a self-funded student with a two-year deadline. I successfully completed my dissertation on time and on budget, but my thesis was distilled down to an acceptability study on what diabetic information users would like to receive, and what mobile health platform they would be most receptive to; I never even got as far as designing an app.

This process taught me that research is a game of inches, not yards, and to develop something as seemingly simple as an app requires a roadmap of many smaller milestones. This roadmap consists of usability, acceptability and feasibility studies, to determine whether there is a need for the intervention, and if people believe that said intervention is useful and usable. Only then can the intervention be piloted and scaled up so that the actual health impact of the intervention can be evaluated.

The studies that make up this PhD dissertation have been conducted over 5 years, with various implementation and technical partners, which has allowed me to work through this entire development roadmap for digital interventions for HIV self-testing. In this PhD, I present studies on the usability, acceptability and feasibility of both the HIV self-tests and digital interventions, including an app that was scaled up and evaluated for its impact in a clinical setting, then investigate what steps must be taken for further scale-up and impact.

CHAPTER 1. General Introduction

Since 1980, human immunodeficiency virus (HIV) has claimed over 40 million lives, making it an international public health priority. Globally, there are almost 39 million people living with HIV, but, the majority of the disease burden is in sub-Saharan Africa, where there are over 25 million people living with HIV. There is currently no cure for HIV, but anti-retroviral therapy (ART) can be taken by people living with HIV to reduce their viral load. When the viral load is undetectable, it can reverse symptoms, repair the immune system and prevent the transmission of the virus to others [1].

The benefits of ART have led to the UNAIDS global HIV 95-95-95 strategy for ending HIV by 2030. This strategy aims that 95% of people living with HIV know their positive status, 95% of those aware of their positive status are linked to treatment for ART, and that 95% of those on ART experience suppressed viral load [2]. In order to achieve these targets, and introduce people to the HIV cascade, a person must first test for HIV. Traditional facility-based testing services were not enough to reach the 90-90-90 targets for 2020, so innovative new testing methods are needed to expand access to testing, especially for key populations [3].

HIV self-testing (HIVST) has been proposed as one of these innovative new methods, as HIVST allows a person to test independent of a healthcare facility, which may remove barriers around stigma and facility access. This move away from facilities, however, may introduce challenges around the counselling, reporting results and linkage to care [4]. Digital health tools have been used for a variety of disease verticals, and digital interventions for HIVST are starting to be developed to address the challenges associated with HIVST [5].

HIV Background

The first cases of what is now referred to as Acquired immunodeficiency syndrome (AIDS) were documented by physicians in California and New York, in the summer of 1981. The physicians observed clusters of previously healthy, young homosexual males that presented with rare opportunistic infections, including Kaposi sarcoma and Pneumocystis carinii pneumonia. Although there was no known cause, the infected persons all experienced a substantial reduction of circulating CD4+ T cells, which resulted in the decreased cell-mediated immunity that was allowing the opportunistic infections to thrive [1,6].

At that time, the human T-lymphotrophic virus (HTLV-I and HTLV-II) was the only known virus to target CD4+ T cells, and it exhibited a very similar transmission patten to that seen in patients with AIDS. This connection eventually led to an association between retroviruses and AIDS, then in 1984, a specific retrovirus, HIV was identified as the cause of AIDS. HIV is genetically linked to a virus that naturally infects primates in Africa, called the simian immunodeficiency virus (SIV). It is generally accepted that the origins of HIV were from cross-species transmission events of the

SIV between primates and chimpanzees, then from chimpanzees to humans in the West African area of Cameroon [7].

HIV-1, the most common variant, is prone to reverse-transcriptase errors, which means that the virus evolves at an exponential pace, resulting in rapid genetic changes that can be used to trace the origins of the virus. Phylogenetic analysis of HIV-1 suggests that the initial transmission to humans happened sometime before 1930, then continued to spread and diversify in the Kinshasa region of the Democratic Republic of Congo, then called Leopoldville [7].

HIV is a blood-borne virus, so it can be spread through the bodily fluids (blood, semen, vaginal fluids, breast milk) of an infected person, and the most common form of transmission is from unprotected sexual intercourse with an infected person. Transmission cannot occur through oral fluids from kissing or sharing food, however it can be spread from mother to baby during birth, by sharing infected needles or through blood transfusions with infected blood donations [1,8]. Although there is no cure for HIV, ART is available for people living with HIV, and when taken as prescribed, ART can make a person's viral load so low that it is undetectable. ART treatment can rebuild the immune system, essentially removing any HIV or AIDS-related symptoms and complications, while also preventing the transmission of HIV to others [9].

HIV lifecycle and treatment

HIV is a retrovirus, which is a type of virus that does not have its own DNA, and instead must infect a host cell to replicate. Retroviruses consist of an RNA strand and some proteins, including an enzyme, reverse transcriptase, that can produce DNA copies of the RNA strand, once inside a host cell. HIV is therefore unable to replicate by itself, and specifically infects CD4+ T cells as their host cell to facilitate replication [10].

During infection, the HIV virus binds and fuses to the CD4+ T cell membrane and releases its contents into the host cell. The reverse transcriptase enzyme uses the host cell's resources to create a strand of HIV DNA by reverse transcribing a complimentary strand of RNA. The viral DNA then enters the nucleus, where another viral enzyme, integrase, incorporates the viral DNA into the host DNA, where it replicates, creating more copies of the viral RNA. The new copies of viral RNA are used to make new copies of the viral proteins, then the RNA and proteins migrate to the cell surface where they break off to create new immature versions of HIV. The virus then matures and becomes infectious when protease cleaves the newly synthesized viral proteins into their final, active form which are called virions. The entire process takes less than 72 hours, and in that time, the infected CD4+ T cell will produce approximately 300 new infectious HIV virions, which then go on to infect new CD4+ T cells, perpetuating the cycle [10].

Anti-retroviral drugs (ARVs) have been developed to stop the propagation of HIV by blocking the replication of the HIV virus at one of six points during the lifecycle. For example, nucleoside reverse transcriptase inhibitors (NRTIs) like Lamivudine (3TC) block the reverse transcription of the HIV RNA, while protease inhibitors (PIs) like Ritonavir (Norvir) blocks the final cleaving of the HIV proteins to activate them. There are over 30 ARVs across six distinct drug classes and Zidovudine (azidothymidine, AZT), a NRTI, was the first drug approved by the FDA for the treatment of AIDS in 1987 [9].

AZT was initially developed in the 1960's as an anti-cancer drug, however it was ineffective and shelved until the mid 1980's, when the manufacturer, Burroughs Wellcome, began testing everything they could against the new HIV virus. They discovered that when AZT was introduced to HIV-infected animal cells, the drug was able to block the activity of the virus, which led to further research and the FDA approval a mere 20 months later [12]. The initial results from the preliminary AZT safety trial were so strong (one death in the AZT arm versus 19 in the placebo arm) that the clinical trial was halted after just four months, so that the placebo group could also receive the AZT intervention [12].

Although AZT had a very promising initial impact, it was not perfect, and the viral load of many patients eventually began to increase. The reverse-transcription errors that made the phylogenetics of the virus easy to track, unfortunately also allowed the virus to evolve and build resistance to medications. In the mid-1990s, protease inhibitors were developed, and combination therapies, known as highly active antiretroviral therapies (HAARTs) drastically reduced the morbidity and mortality associated with HIV and AIDS. HAART treatment typically consisted of three different medications referred to as an *AIDS cocktail*, until treatment was simplified in 2006, when three fundamental ARVs (efavirenz, emtricitabine and tenofovir) were combined into one single fixed-dose pill, called Atripla [9].

HAARTs were highly effective, however, the cost of these medications still made them inaccessible to many populations. The initial cost of a one-year dose of AZT was US$ 8,000 but in 2003, the President's Emergency Plan for AIDS Relief (PEPFAR) committed US$ 15 billion over five years to help distribute ARVs to resource limited nations with high HIV disease burdens. Despite this financial commitment, ART was still not readily made available to all patients due to concerns regarding cumulative drug toxicity from long-term use [13]. Although ARVs were effective at reducing the morbidity and mortality for people living with HIV, treatment was expensive and potentially toxic, so the prioritisation of preventative measures was also needed to stop people from becoming infected with HIV in the first place.

HIV prevention

The majority of new HIV infections are through anal or vaginal sex with an infected person, so most prevention programmes focus on reducing HIV the same way they address other sexually transmitted infections (STIs). This includes education, awareness and advocacy for safe sex, including abstinence, consent, condom use and reducing risky sexual behaviour. While these preventative measures are encouraged for all STIs, there are additional measures that can be taken to reduce the chances of getting HIV, specifically. Voluntary male medical circumcision (VMMC) can lead to a 60% reduction of HIV for males in a high incidence setting [14], and pre-exposure prophylaxis (PrEP), a type of anti-retroviral medication, can reduce the risk of getting HIV from sex by 99% [15].

Furthermore, if a person living with HIV takes their ART as prescribed, they should experience a reduced viral load, and when their viral load is undetectable (below 200copies/ml), they can no longer transmit HIV to their sexual partner. When a person living with HIV keeps their viral load undetectable in order to not transmit the virus, it is referred to as treatment-as-prevention (TasP). TasP was documented in the 2011 HPTN-052 trial, then confirmed by several large-scale cohort studies, which eventually led to the U=U campaign (undetectable = untransmittable), endorsed by the WHO in 2016 [16].

TasP was one of the primary rationales for the universal test and treat (UTT) strategy. The UTT strategy recognised the value of using ART for prevention through early treatment and viral load suppression, so in 2015 the WHO released new ARV guidelines that removed clinically low CD4+ counts as a requirement for ART initiation [16]. Initially, treatment was delayed for asymptomatic patients based on their CD4+ count, and in the early 2000s, patients could only start ART when their CD4+ count dropped below 200 cells/mm^3. In 2009, most international guidelines relaxed the threshold to 350 cells/mm^3, then in 2013, they loosened the threshold to 500 cells/mm^3 before finally removing the requirement all together in 2015 [13].

This now widespread approach of starting ART at HIV diagnosis, regardless of CD4+ count or disease stage, ensured that everyone has the opportunity to quickly suppress their viral load, which should reduce the transmission of HIV, and therefore reduce HIV incidence as well [17]. Early initiation of treatment and UTT have been shown to increase the life expectancy of people living with HIV, while also reducing the transmission of the virus to HIV negative partners by 96% [18].

HIV testing services

Although CD4+ counts are no longer required to initiate ART, a person must still conduct an HIV test before they can initiate treatment, as HIV tests are the first contact point for people entering

the HIV care cascade. People that test negative are provided access to preventative treatment and education, while people that test positive are linked to care and ART treatment.

The first HIV tests were made available in 1985, just one year after HIV was identified as the cause of AIDS. The first-generation tests were enzyme-linked immunosorbent assays (EIA) that could detect IgG antibodies six to 12 weeks after HIV infection, however false positives were common. Due to the false positives, HIV testing algorithms required a second confirmatory test with a Western blot assay or an immunofluorescence assay (IFA). Second and third-generation tests reduced the latency window to only three weeks by adding IgM detection and recombinant agents. With subsequent generations, the window period was reduced to two weeks, and false positives were reduced but not eliminated [19].

Although newer generation assays reduced the window period, all EIAs had to all be conducted in a laboratory setting, which meant that it took weeks for a person to learn their results. One-third of testers from public facilities did not return to collect their results and were lost to follow-up before learning their HIV status. To address this attrition, rapid diagnostic tests (RDT) were developed, which used a small oral fluid or blood specimen to reveal the result in minutes, not weeks. In 2003, OraQuick was waived by the Clinical Laboratory Improvements Amendments Law, and it became the first RDT approved for use outside a traditional laboratory setting. This allowed a person to conduct a point of care test at a clinic or doctor's office, where they could receive their result in just a few minutes, which significantly reduced loss to follow-up. [20,21].

Despite the growing availability of immediate results, HIV testing services were still not being accessed by everyone, as several structural and individual barriers to care remained. These barriers included direct and opportunity costs, the time needed to access testing services, as well as the fear of stigma and discrimination associated with a positive result. These barriers unproportionally effected key populations and their partners, including men who have sex with men, people who inject drugs, and female sex workers. Although key populations make up a small percentage of the populace, over half the new HIV infections are among key populations, so testing strategies need to remove barriers associated with these populations [22].

HIV self-tests (HIVST) are a type of RDT that allows a person to test themselves privately and independently for HIV, by collecting and testing their own oral or blood specimen, outside of a healthcare facility. By removing the test from a healthcare facility, HIVSTs can complement traditional HIV testing programs by removing barriers associated with stigma, costs and time to access traditional testing [22}. Despite their ability to enhance testing programmes, especially for key populations, HIVSTs still present challenges surrounding pre and post-test counselling, reporting results and linking positive cases to ART. Digital interventions for HIVST have been

proposed as a way to address these challenges, but little is known about their usability, performance or efficiency, when used to optimise HIV testing services [5].

Research questions

The aim of this thesis is to investigate the use of HIVSTs and explore the introduction of digital interventions for HIVSTs as a way to improve HIV testing services.

1. Are HIVSTs a usable, acceptable and feasible option to enhance HIV testing services in South Africa?
2. Can digital interventions be developed and used to compliment HIVST programmes?
3. Can digital interventions for HIVSTs improve health impact in South Africa?
4. Should digital interventions for HIVST be scaled-up, and if so, how?

These research questions are investigated in South Africa, a LMIC that has the highest HIV burden in the world.

Outline of the thesis

This thesis is broken down into three parts: (1) HIV Self-testing and digital intervention justification (chapters 2-5); digitally assisted HIV self-testing (chapters 6-8) and (3) consent and regulation as future considerations (chapters 9-11). In Part 1, chapters 2 and 3 confirm the performance of HIVSTs in South Africa, as well as their usability and acceptability, then chapters 4 and 5 present evidence for the use of digital interventions to compliment linkage to care for HIV and highlights the increased acceptability of digital health tools due to the COVID-19 lockdown. Chapters 6-8 in Part 2 provide examples of digital interventions that have been developed to help users in South Africa conduct HIVSTs and link to care. These chapters show that digitally assisted self-testing is accepted by users, and that they can improve testing efficiency in facilities. In Part 3, chapter 9 summarizes the current information on HIVST and digital interventions for HIVST, then chapters 10 and 11 provide future considerations for their scale-up, emphasizing informed consent and WHO regulation.

In Chapter 2, we contextualize the HIV testing and treatment landscape in sub-Saharan Africa and introduce HIVSTs as a way to improve testing. The WHO's *90-90-90* initiative required 90% of people with HIV be aware of their status by 2020, but in South Africa, conventional facility-based testing had only reached 84.9% by 2018. Innovative new testing methods, like HIVST had been suggested as a way to close the testing gap, but there was no evidence to show that lay-persons in south Africa would be able to perform a self-test unassisted. This study was conducted with 1400 adults in Johannesburg to evaluate the usability of seven HIVSTs. Participants were given a self-test kit, with no further information about the device or procedure, and asked to

perform the test in front of an observer. The observer used questionnaires to compose a usability index based off a HIVST process checklist, a contrived results interpretation and a post-test interview [23].

Chapter 3 builds off the usability of HIVSTs by investigating the performance of these devices as directed by the WHO prequalification literature. At the time of investigation, various HIVST kits had been developed; however, in many countries, their entry into the market was contingent on either being listed as WHO prequalified diagnostics/products or being approved by that country's health device regulator or both. This cross-sectional study was intended to provide evidence for WHO prequalification by evaluating the usability, sensitivity and specificity of four HIVSTs in Johannesburg by providing users with a boxed, sealed HIVST kit and no further instruction. Uses performed the test under observation, where a checklist was used to calculate a usability index, while the sensitivity and specificity of each HIVST were calculated by comparing the HIVST results to the 'gold standard' ELISA laboratory blood test [24].

While the previous two chapters describe self-testing, chapter 4 introduces digital interventions and explores them in the context of the second *90-90-90*, which is that 90% of all people living with HIV should be on ARVs. South Africa provides free antiretroviral therapy for almost 5 million people living with HIV, but only 71% of the eligible people are on treatment. Many LMICs, like South Africa have expanded access to smartphones, and digital health apps may improve this cascade. We developed and tested a digital health app for Android smartphones, SmartLink, which provided HIV-related laboratory results, information, support, and appointment reminders intended to empower patients and link them to care. This multisite randomized controlled study was conducted in Johannesburg, where the control arm received the standard of care, which was a referral to a treatment site, while the intervention arm received the standard referral as well as the app. Linkage to care was confirmed by an HIV-related blood test reported on the National Health Laboratory Service database between 2 weeks and 8 months after initiation [25].

In chapter 5, we investigate how the COVID-19 lockdown changed peoples' perceptions and use of digital health technologies. Due to this lockdown, individuals were forced to find and use alternatives for accomplishing tasks including shopping, socializing, working, and finding information, and it was believed that many turned to the internet and their mobile devices to accommodate this change. This study aimed to describe how South Africans consumed and internalized information surrounding the COVID-19 outbreak to determine whether the COVID-19 lockdown had influenced technology behavior, particularly in terms of health communication and information. To investigate this, people in South Africa were invited to complete an online survey from June 24 to August 24, 2020, which collected information on demographics, technology use during the lockdown, and COVID-19 knowledge [26].

In chapter 6, we build from our existing knowledge of HIVSTs and digital health apps from previous chapters and introduce our first digital intervention for HIVST. Although HIVST reduces barriers associated with facility-based testing, there is no formal mechanism for users to self-report results or link to care. Apps Like SmartLink have been shown to link users to care after facility-based testing, so the Aspect™ HIVST app was developed with the intention to report results, and link users to care after self-testing in South Africa. This cross-sectional pilot evaluated the acceptability and feasibility of the Aspect™ HIVST app for individuals from the inner-city of Johannesburg. Participants were given an OraQuick HIVST kit and a smartphone preloaded with the app, then asked to follow the in-app instructions to complete the HIVST and upload results. Trained HCWs observed and recorded any deviations from the instructions, and conducted a post-test survey to assess acceptability. Feasibility was evaluated as the number of agreeing participants that completed the self-test, and uploaded all information onto the app correctly [27].

While the previous feasibility study was conducted in a clinical setting, under the observation of HCWs, it did not investigate the reporting of results in a real-life setting as an outcome. Chapter 7 investigates Ithaka, an app that was developed to close this knowledge gap by providing untrained HIVST users a digital intervention to accompany their HIVST, independent of a formal clinical setting, while also removing the potential for observational bias. The objective of this study was to investigate the use of Ithaka as an HIVST support tool for individuals, specifically the ability to report self-results outside a clinical environment. At existing HIVST distribution sites, individuals were given HIVST kits, then invited to log into a reverse-billed app. Participants could test at home and report their results through the app anytime. The app tracked when people logged-on, registered, received counselling and reported results [28].

Now that digital interventions for HIVST have been investigated for usability in the real world, chapter 8, investigates whether their use can improve health outcomes and impact. Facility-based testing is the most common method of testing, but limited workspace and human resources are challenges that digitally supported HIVST overcome, while also potentially empowering the client as well. The study objective was to determine the feasibility of integrating digitally supported HIVST into clinics, then describe HIV testing volume, populations reached, and ART initiation [29].

In chapter 9 we chronicle the history of HIVST, including the associated challenges, then explore the evolution of digital interventions for HIVST as a way to overcome said challenges. This chapter summarises the current body of knowledge surrounding HIVST, and illustrates how findings from

the previous chapters build off of each other to show that digital interventions for HIVST are usable, acceptable and feasible as a way to improve testing efficiency in South Africa [30].

In chapter 10, we introduce and examine informed consent forms (ICFs), something that is not exclusive to just HIV or digital tools; however, in this context they are of great importance, especially when taking data privacy into consideration. ICFs are used to obtain consent from participants, but the complexity and comprehensiveness of these forms may not always be appropriate. Readability can be quantified by readily available formulas, like the Flesch Reading Ease test, which the South African ethics guidelines suggest should be used to assess the complexity of ICFs, with an appropriate score being equivalent to the grade 8 reading level, or lower. In this study, we used readability formulas to determine whether current South African ICFs are appropriate for the general population by investigating a sample of English ICFs which received approval from local ethical review boards during the past 5 years [31].

Chapter 11 explores the future of digital interventions for HIVST by examining software as a medical device (SaMD), and the fragmented systems for regulating or approving these interventions. We introduce the WHO Prequalification Program and explores whether the programme could be used to prequalify digital interventions for HIVST by presenting arguments for and against prequalification [32].

The general discussion is presented as chapter 12, which includes a description of the previous chapters' main findings. We then provide context to these findings by describing the strengths and limitations, then discuss the implications of our findings to HIV testing and the greater scientific community through future research.

Gender, diversity and inclusion statement

The author of this thesis understands that he is a cis-gendered, white male from a from a high-income country, studying at a university in a high-income country, which does not represent a lot of diversity. Although the body of research presented here was conducted in South Africa, a low- and middle-income country (LMIC), the author does not condone extractive research, and has taken great strides to ensure that an inclusive, capacity building approach was employed. To ensure this, the author has adopted a team science approach and completed this research while living and working in sub-Saharan Africa, and all of the associated research organisations have given their permission for these publications to be included in this thesis.

The team science approach has allowed for the learnings, experiences and benefits realised by this research process to be shared with local communities, to ensure that capacity building and funding was realised by local researchers and institutions as well. The ten publications in that

make up this thesis consist of 65 authorships, included 41 authorships from sub-Saharan Africa, and 30 female authorships. Furthermore, to ensure a wide dissemination of findings, all of the papers were published in open-access journals, including five publications in journals local to sub-Saharan Africa.

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Part 1. HIV Self-testing and digital intervention justification

CHAPTER 2. Usability assessment of seven HIV self-test devices conducted with lay-users in Johannesburg, South Africa

This chapter is based on:

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Abstract

Introduction

The first 90 of the *90-90-90* initiative introduced by the World Health Organization (WHO) in 2015 requires 90% of people with HIV be aware of their status by 2020. In South Africa, conventional facility-based testing had reached 84.9% in 2018; innovative new methods, like HIV self-testing (HIVST) may close the testing gap. This study aimed to determine the usability of seven HIVST kits among untrained South Africans.

Methods

This cross-sectional study of 1400 adults in Johannesburg evaluated the usability of five blood fingerstick and two oral fluid HIVSTs, using WHO prequalification criteria, from June 2016 to June 2018. Participants were handed one kit, with no further information about the device or test procedure, and asked to perform the test in front of an observer. The observer used product-specific semi- structured questionnaires organized into a composite usability index (UI) using a HIVST process checklist, a contrived results interpretation and a post-test interview that expanded on participant experiences with the device and instructions-of-use (IFU). Participants were not tested themselves, but provided with contrived results to interpret.

Results

The average UI was 92.8% (84.2%-97.6%); the major difficulty was obtaining and transferring the specimen. Participants correctly interpreted 96.1% of the non-reactive/negative, 97.0% of the reactive/positive, 98.0% of the invalid and 79.9% of the weak positive results. Almost all participants (97.0%) stated they would visit a clinic or seek treatment for positive results; with negative results, half (50.6%) stated they should re-test in the next three months while one-third (36.1%) said they should condomize. Nearly all found the devices easy to use (96.6%), the IFUSs easy to understand (97.9%) and felt confident using the test unassisted (95.9%) but suggested improvements to packaging/IFUs to further increase usability; 19.9% preferred clinic-based testing to HIVST.

Conclusion

The UI and interpretation of results was high and in-line with previous usability studies, suggesting that these kits are appropriate for use in the general, untrained and unsupervised public.

Introduction

HIV testing and counselling (HTC) represents the first '90' of the *90-90-90* initiative [1] and in South Africa 84.9% of adults living with HIV know their HIV status, however there are concerns that South Africa will not reach this 90% target by 2020 [2]. Established facility-based testing presents barriers to accessing HTC [3–5], and innovative new methods like HIV self-testing (HIVST) are needed close the test gap by reducing barriers for priority populations [6–8]. HIVST refers to a process in which a person performs their own HIV test; which may be more convenient, require less travel and waiting time, and be more private [9–11].

Initially, home-based HIV tests required the user to send a blood sample to a laboratory, then wait days or weeks for results; however modern HIVST rapid diagnostic tests (RDTs) can provide results in minutes, without a laboratory [12]. In 2012 the Food and Drug Administration in the United States approved OraQuick ADVANCE Rapid HIV-1/2 Antibody Test as the first-ever over-the- counter HIVST RDT, including individuals without any prior experience in HIV testing [13].

Growing evidence from different contexts supports the acceptability and usability of HIVST [14–17] and guidelines suggest that only validated products be used for programmes. Since then, 40 countries, including South Africa, have incorporated HIVST in national policies [18] and the South African National Department of Health will only permit the use of WHO pre-qualified products to be used in public health programmes [19]. The WHO prequalification (PQ) process was designed in accordance with international standards, which includes assessing clinical performance among a broad range of self-testing users, with studies that compare the device to a suitable reference standard test [20].

The HIV Self-Testing Assessments and Research (HSTAR) programme, supports HIVST developers in the PQ process, by independently providing data on usability. The purpose of this study was to determine the usability of seven prospective HIVSTs in the hands of untrained, intended users in line with the specifications set out by WHO in the abovementioned prequalification document.

Methods

Study design

This usability evaluation was a cross sectional study that used convenience sampling to recruit consenting adults from the general population in the inner-city of Johannesburg, South Africa from June 2016 until June 2018. Using WHO PQ guidance, this study evaluated the usability of seven HIVSTs that were in varying stages of development for the South African market. The HIVST devices were evaluated independently and in series, with one device evaluation finishing before the next started. No participants were enrolled for more than one device.

HIVSTs

To simulate the real world experience, each HIVST device being evaluated was presented in shelf ready packaging (similar to other devices already approved for distribution within South Africa), using the manufacturer's instructions for use (IFU) and kit components. Seven HIVST devices were assessed: five fingerstick whole-blood (FS) devices and two oral fluid (OF) devices. The five FS devices were produced by Atomo Diagnostics (Australia) (two devices; generation 1 and generation 2), Biolytical Laboratories (Canada), Biosure Ltd (United Kingdom), and Chembio Diagnostic Systems (USA), while the two OF tests were produced by Calypte Biomedical Corporation (USA) and Orasure Technologies (USA).

Study participants

Based on the WHO prequalification documents, a sample size of 200 participants [20] was suggested for the usability assessment of each device (1400 total participants). Recruiters were made conscious during training that the study aimed to include diverse age groupings and education levels, as well as equal gender participation [20].

Participants were included if they were 18 years and older, able to read English, first-time HIV self-testers, willing to provide oral fluid or fingerstick blood samples (according to which test was being evaluated) and reported an unknown HIV status. Healthcare workers (including lay counsellors who do HIV testing), any person who had any prior experience with HIV self-testing, persons who had received an experimental HIV vaccine or were taking HIV pre-exposure prophylaxis, and persons known to be HIV positive or have any extenuating condition which may interfere with the process (such as poor vision or intoxication) were excluded. Participants were registered onto a Biometric Enrolment System, which uses fingerprint scanning to eliminate the chance of duplicate enrolment.

Pilot

At the time of evaluation, no verified or standardized questionnaires for investigating the usability of HIVSTs for prequalification were available, so a product-specific semi-structured questionnaire was developed based on the WHO PQ literature [20–23]. The questionnaire was piloted in a sample of 50 participants for each HIVST device. Findings were shared with the manufacturers, and they were encouraged to incorporate the feedback into their final product for evaluation [16,24]. Not all manufacturers chose to amend their end product, but in some cases, there were major edits to their IFU to ensure clarity and the successful performance of critical steps.

In order to evaluate participants' actions and perceptions regarding usability, the questionnaire was organized into three parts: a usability index guided by a HIVST process checklist; the

interpretation of contrived results; and a post-test interview that assessed the participants' competency and experiences, while also inviting recommendations (see supporting information S1 Data Collection Checklists)[1].

Data collection

Participants were handed a "packaged" kit, including the IFU, with no further information about the device or test procedure, then asked to perform the test in front of an observer, who monitored each step of the test for success, confusion, difficulty and errors. The observer remained silent throughout and did not provide any assistance or interference. To document each participants' actions, an observer used a product-specific semi-structured questionnaire, which included a product-specific checklist and a post- test interview. As this study only evaluated usability, not performance of the HIVST, the HIVST devices were removed after the final processing step (before results could be observed) and substituted for contrived tests that were developed by each manufacturer. Participants were provided with four contrived devices (non-reactive/negative, reactive/positive, weak positive and invalid), serially and in random order, that displayed the possible results and asked to interpret each result.

Usability index

Prior studies often describe usability qualitatively, as a way to provide feedback that can be incorporated into future designs, however at the time of this study, there were no validated data collection tools to quantify usability [22,23]. A product-specific HIVST process checklist was developed to calculate a usability index that could be applied to each of the HIVSTs independently. This usability index was motivated by previous HIVST briefing documents from the Blood Products Advisory Committee [25], which quantified operational error rates by identifying and tracking errors based on the IFU. Instead of tracking erroneous steps to identify the error rate (expressed as a percentage), this study tracked successful steps, in order to identify usability with the usability index, which was also expressed as a percentage. The checklist and steps used to calculate each usability index was product-specific, so direct comparisons between HIVSTs could not be made.

In order to calculate the usability index, a device and IFU assessment of each HIVST was used to create a product-specific yes/no checklist of all steps for the HIVST procedure, which ranged from 10 to 17 questions. A trained observer used the checklist to document each participants' usability of the HIVST by tracking the number of successful participants that completed each step, which was presented as a frequency and percentage. For steps with negative inflection, the 'No' response was the value used towards the final usability index (ie. *Was it difficult for the*

[1] https://doi.org/10.1371/journal.pone.0227198.s001

participant to remove the test device from the pouch?). The successful usability percentages of each step were then averaged, to provide the usability index for each device, from 0% (unusable) to 100% (highly usable) [26,27].

Interpreting contrived results

To evaluate the participant's ability to interpret the device results, contrived tests were provided by each manufacturer to represent the four possible test outcomes: 1) non-reactive/negative, 2) reactive/positive, 3) weak positive, and 4) invalid (no control). Observers used a yes/no checklist to document whether the participant noted the control line and the test line, then whether their interpretation of the results was correct. They rated the participants' apparent level of confidence and satisfaction, whether the participant appeared calm, nervous, verbally distressed or confused, and whether staff intervention was requested.

HIV test results were not recorded or reported to participants. Participants who wished to have a HIV test were referred to the nearby clinics adjacent to the study sites, where testing is readily available; this is conventional practice in similar studies where HIV results are not made known to participants, for research design reasons, and is a local ethics board requirement.

Post-test interview

As part of the post-test interview, participants were asked what to do following both positive and negative results, in order to evaluate how well the participant understood the IFU recommendations for each type of test result.

The post-test interview evaluated each participant's comprehension of the IFU and packaging information, whether they would use the test again or recommend it to a friend, and experiences throughout the testing process. Open-ended questions asked for comments and recommendations for their test device.

Data analysis

Data were transcribed from the product-specific semi-structured questionnaire into an excel database by field workers. Quantitative data was analyzed with descriptive statistics in Excel. Qualitative data on usability and experiences were categorized and assessed to provide context and supplement the quantitative results.

Ethical considerations

The Human Research Ethics Committee of the University of the Witwatersrand provided approval for the study (No. 160306). Once approved, the protocol was registered with the National Human Research Ethics Committee (www.ethicsapp.co.za), the South African National Clinical Trial

Registry (www.sanctr.gov.za) and ClinicalTrial.gov. Trained study staff obtained written informed consent from all study participants using an information sheet and informed consent document approved by the Wits HREC. The informed consent form was translated into English, Zulu, Sotho and Xhosa. Participants were given no incentives or reimbursements for their participation in the study.

Results

While the majority of trial participants were South African (1025/1400(73.0%);58.0%-94.5%), a substantial minority of Zimbabweans and other Africans participated in some of the evaluations. Participant age ranges were evenly distributed with approximately one third being 18–25 years old (493/1400 (35%); 18.5%-65.0%), 26–35 years old (471/1400 (34.0%); 15.0%-44.0%) and over 35 years old (435/1400 (31.0%); 17.5%-48.5%), respectively. Education levels were also distributed relatively evenly, between secondary school (499/1400 (36.0%); 33.5%-41.0%), tertiary (478/1400 (34.0%); 33.0%-37.5%) and primary (423/1400 (30.0%); 25.0%-33.0%). school (499/1400 (36.0%); 33.5%-41.0%), tertiary (478/1400 (34.0%); 33.0%-37.5%) and primary (423/1400 (30.0%); 25.0%-33.0%). These demographics are summarised in Table 1.

Table 1. Participant demographics.

Demographic	Biosure n (%)	INSTI n (%)	Atomo1 n (%)	Atomo2 n (%)	Chembio n (%)	Orasure n (%)	Calypte n (%)	Total n (%)
Total n	200 (100.0)	200 (100.0)	200 (100.0)	200 (100.0)	200 (100.0)	200 (100.0)	200 (100.0)	1400 (100.0)
Nationality								
South African	129 (64.5)	139 (69.5)	136 (58.0)	189 (94.5)	173 (86.5)	132 (66.0)	127 (63.5)	1025 (73.0)
Zimbabwean	63 (31.5)	55 (27.5)	47 (18.0)	9 (4.5)	21 (10.5)	61 (30.5)	50 (25.0)	306 (22.0)
Other	8 (4.0)	6 (3.0)	17 (19.0)	2 (1.0)	6 (3.0)	7 (3.5)	25 (12.5)	71 (5.0)
Sex								
Female	91 (54.5)	104 (52.0)	88 (44.0)	90 (45.0)	80 (40.0)	86 (43.0)	94 (47.0)	633 (44.5)
Male	109 (54.5)	96 (48.0)	112 (56.0)	110 (55.0)	120 (60.0)	114 (57.0)	106 (52.0)	777 (55.5)
Age								
18-25 years old	37 (18.5)	54 (27.0)	66 (33.0)	110 (55.0)	130 (65.0)	42 (21.0)	54 (27.0)	493 (35.0)
26-35 years old	88 (44.0)	77 (38.5)	81 (40.5)	55 (27.5)	30 (15.0)	61 (30.5)	80 (40.0)	472 (34.0)
Over 35 years old	75 (37.5)	69 (34.5)	53 (26.5)	35 (17.5)	40 (20.0)	97 (48.5)	66 (33.0)	435 (31.0)
Education Level								
Primary school or less	65 (32.5)	66 (33.0)	60 (30.0)	50 (25.0)	51 (25.5)	66 (33.0)	65 (32.5)	423 (30.0)
Secondary school	67 (33.5)	67 (33.5)	74 (37.0)	82 (41.0)	74 (37.0)	67 (33.5)	68 (34.0)	499 (36.0)
Tertiary school (any)	68 (34.0)	67 (33.5)	66 (33.0)	68 (34.0)	75 (37.5)	67 (33.5)	67 (33.5)	478 (34.0)

n-number; %-percentage

Usability index

The average usability index for all seven HIVSTs was 92.8% (84.2% to 97.6%). Each HIVST has been described individually in further detail below (Table 2) (slightly adapted from the original

questionnaire for ease of presenting the results), while the complete datasets for each HIVST are available as supporting information S1[2], S2[3], S3[4], S4[5], S5[6], S6[7] and S7[8] Datasets.

Biosure

The overall usability index of Biosure was 84.2%. Nearly all participants (193/200;96.5%) read and used the IFU and 23(11.5%) participants experienced difficulties opening the packaging. Twenty one (10.5%) participants had difficulties lancing their finger, while 37(18.5%) participants had difficulties forming a blood droplet, which resulted in only 156(78.0%) participants able to fill the tube with an adequate amount of blood during specimen collection. Approximately one quarter of participants had trouble placing the buffer pot upright in the slot (52/200;26%) and were unable to push the test tube to the bottom of the buffer pot (47/200;23.5%). Despite any missed or incorrect steps, 178(89.0%) participants got to the last step.

INSTI

For INSTI, the overall usability index was 97.4%. All (200) participants read and used the information sheet and 10(5.0%) had difficulty removing the device from the packaging. All participants were also able to remove the cap of Bottle 1 and the lancet. With respect to specimen collection, 194(97%) participants correctly massaged their finger, 198(99%) correctly lanced their finger, 188(94%) participants were able to form a bold droplet, and 171(88.5%) were able to successfully transfer the droplet into Bottle 1. Two (1.0%) participants had difficulties capping Bottle 1, seven (3.5%) participants did not shake the bottle the required four times, and only two (1.0%) participants were unable to pour the liquid from Bottle 1 into the device and wait until it disappeared. Similarly, seven (3.5%) participants did not shake the second or third bottle four times, and two (1.0%) participants did not pour the liquid from Bottle 2 or Bottle 3 into the device and wait until it disappeared. Despite any missed or incorrect steps, 199(99.5%) participants completed the entire process.

Atomo1

The usability index for Atomo1 was 89.1%. All 200 participants read and used the information sheet and only 2(1.0%) experienced difficulty removing the device from the pouch, however 64(32.0%) were unable to correctly place the device once removed. During specimen collection, all the participants were able to prime the lancet and correctly massage their finger, however

[2] https://doi.org/10.1371/journal.pone.0227198.s002
[3] https://doi.org/10.1371/journal.pone.0227198.s003
[4] https://doi.org/10.1371/journal.pone.0227198.s004
[5] https://doi.org/10.1371/journal.pone.0227198.s005
[6] https://doi.org/10.1371/journal.pone.0227198.s006
[7] https://doi.org/10.1371/journal.pone.0227198.s007
[8] https://doi.org/10.1371/journal.pone.0227198.s008

5(2.5%) participants did not successfully prick their finger and 19(8.5%) did not squeeze their finger hard enough to create a blood droplet; this led to only 126(64%) participants filling the blood tube with the correct volume of blood. One hundred and eighty-one (90.5%) participants flipped the blood tube into the well but only 126(63.0%) ensured that the blood successfully moved into the well. The 3 drops of buffer were added correctly by 182(91.0%) participants and the test fluid ran across the strip for 185(92.5%) participants. A total of 187(93.5%) participants completed the entire process, despite any missed or incorrect steps.

Atomo2

The Atomo2 usability index was 97.6%. Each of the 200(100%) participants read and used the information sheet and only one (0.5%) had difficulty removing the device from the package. For specimen collection, all participants were able to remove the tab on the lancet and push the grey button to prick the finger. Despite only 163(83.0%) participants having correctly massaged their finger to stimulate blood flow, 197(98.5%) participants were able to form a blood droplet and successfully touch the blood droplet to the channel. Fourteen (7.0%) participants did not produce enough blood to adequately fill the channel, but 198(99.0%) participants were able to press the button to activate the test and the fluid successfully ran across the strip of all but one (0.5%) test. Despite any missed or incorrect steps, all of the participants (200/200;100%) completed the entire process.

Chembio

The usability index for Chembio was 93.7%. Almost all participants (198/200;99.0%) read and used the information sheet, while six (3.0%) had difficulty removing the device from the foil package. One hundred and ninety-nine (99.5%) participant successfully set up the stand on a flat surface, while four (2.0%) participants were unable to remove the buffer cap or correctly insert the buffer cap into the test stand. While preparing for specimen collection, six (3.0%) participants did not open the disinfectant wipe, 39(19.5%) had difficulties opening the sterile pad and 10(5.0%) did not disinfect the finger and allow it to dry. While three (1.5%) participants did not push down hard enough to properly prick the skin, almost all participants (198/200;99.0%) successfully uncapped the lancet, correctly placed it against the side of their fingertip and were able to squeeze out the first drop of blood. One hundred and seventy-four (87.0%) were also able to squeeze out a second drop of blood and 194(97.0%) filled the testing device with an adequate amount of blood. After specimen collection, 137(68.5%) participants used the sterile pad to wipe up the blood. Once the specimen was collected, 194(97.0%) participants were able to insert the tip of the device into the test stand opening, 162(81.0%) were able to push firmly through the foil cap (confirmed by 3 snaps) and 175(87.5%) participants checked for the formation of pink stain within one minute of puncturing the buffer pot. A total of 197(98.5%) participants completed the entire process, despite any missed or incorrect steps.

Orasure

For Orasure, the overall usability index was 92.2% and all 200 participants read and used the information sheet. Six (3.0%) participants had difficulty removing the test device from the pouch and 20(10.0%) participants had difficulty removing the test tube from the pouch. Once removed, 196(98.0%) were able to remove the test tube cap, and 151(75.5%) were able to slide it into the stand with no difficulty. Despite 27(13.5%) participants inadvertently touching the flat pad, specimen collection was performed correctly by 152(76.0%) participants and 198(99.0%) were able to place the device in the test tube correctly. Despite any missed or incorrect steps, all of the participants (200) completed the entire process.

Calypte

The usability index for Calypte was 95.5%. All 200 participants read and used the information sheet and only three (1.5%) experienced difficulty removing the test contents from the box. Eighty-one (40.5%) had difficulty inserting the test tube into the box and 24(12.0%) had difficulty pulling the cap off the test tube. For specimen collection, all participants successfully removed the oral brush from the plastic bag, 194(97.0%) correctly used the brush (brush the upper and lower gums twice each) and 199(99.5%) correctly inserted the brush into the test tube when done collection. One hundred and ninety-five (97.5%) correctly pushed the brush up and down in the test-tube (six to eight times), 197(98.5%) correctly squeezed fluid from the brush correctly, then all of the participants correctly removed the brush from the test tube. Once the brush was removed, 198(99.0%) participants properly removed the test strip from the foil pouch and correctly dropped it into the test tube. All 200(100%) participants completed the entire process, despite any missed or incorrect steps.

Table 2. Usability checklist and index.

Usability Checklists	**Yes n (%)**	**No n (%)**	**Usability Index (%)**
Biosure			
1. Did the participant read/use the IFU?	193 (96.5)	7 (3.5)	96.5
2. Did the participant have difficulty removing the test tube from the test pack?	23 (11.5)	177 (88.5)	88.5
3. Did the participant the remove the buffer pot and stand in upright in slot?	148 (74.0)	52 (26.0)	74.0
4. Did the participant have difficulty lancing their finger?	21 (10.5)	179 (89.5)	89.5
5. Did the participant have difficulty forming a blood droplet?	37 (18.5)	163 (81.5)	81.5
6. Was the participant able to fill the tube with adequate amount of blood?	156 (78.0)	44 (22.0)	78.0
7. Was the participant able to push test tube right to the bottom of the buffer pot?	153 (76.5)	47 (23.5)	76.5
8. Was a control line present?	159 (79.5)	41 (20.5)	79.5
9. Did the participant quit the process at any point?	22 (11.0)	178 (89.0)	89.0
10. Did the participant continue the process despite a missed or incorrect step?	178 (89.0)	22 (11)	89.0
Total usability index			**84.2**
INSTI			
1. Did the study participant read/use the information sheet?	200 (100.0)	0 (0.0)	100.0
2. Was it difficult for the participant to remove the test device from the pouch?	10 (5.0)	190 (95.0)	95.0
3. Was the study participant able to remove the cap of Bottle 1?	200 (100.0)	0 (0.0)	100.0
4. Did the study participant twist the tip of the lancet off?	200 (100.0)	0 (0.0)	100.0

5. Did the participant rub his/her finger correctly (up and down/vertical motion)?	194 (97.0)	6 (3.0)	97.0
6. Was the study participant able to lance his/her finger correctly?	198 (99.0)	2 (1.0)	99
7. Was the study participant able to form a blood droplet?	188 (94.0)	12 (6.0)	94
8. Was the study participant able to get the blood droplet to fall into Bottle 1?	171 (85.5)	29 (14.5)	85.5
9. Was the study participant able to twist the cap onto Bottle 1?	198 (99.0)	2 (1.0)	99
10. Did the study participant shake Bottle 1, 4 times?	193 (96.5)	7 (3.5)	96.5
11. Did the study participant pour the liquid from Bottle 1 into device and wait until liquid disappeared?	198 (99.0)	2 (1.0)	99
12. Did the study participant shake Bottle 2, 4 times?	193 (96.5)	7 (3.5)	96.5
13. Did the study participant pour the liquid from Bottle 2 into device and wait until liquid disappeared?	198 (99.0)	2 (1.0)	99
14. Did the study participant shake Bottle 3, 4 times?	193 (96.5)	7 (3.5)	96.5
15. Did the study participant pour the liquid from Bottle 3 into device and wait until liquid disappeared?	198 (99.0)	2 (1.0)	99
16. Did the participant quit the process at any point?	1 (0.50)	199 (99.5)	99.5
17. Did the participant continue the process despite a missed or incorrect step?	199 (99.5)	1 (0.5)	99.5
Total usability index			**97.4**
Atomo1			
1. Did the study participant read/use the information sheet?	200 (100.0)	0 (0.0)	100.0
2. Was it difficult for the participant to remove the test device from the foil pouch?	2 (1.0)	198 (99.0)	99.0
3. Did the study participant massage finger for 5 to 10 seconds?	200 (100.0)	0 (0.0)	100.0
4. Was the study participant able to gently turn and take out the green tab?	200 (100.0)	0 (0.0)	100.0
5. Did the study participant successfully push the grey button in to prick finger?	195 (97.5)	5 (2.5)	97.5
6. Did the participant place the test device in the section allocated on the IFU?	136 (68.0)	64 (32.0)	68.0
7. Was the study participant able to form a blood droplet by squeezing firmly behind the prick site?	181 (90.5)	19 (9.5)	90.5
8. Did the study participant fill the blood tube with the correct volume of blood?	126 (63.0)	74 (37.0)	63.0
9. Was the participant able to flip the blood tube over into the well, successfully?	181 (90.5)	19 (9.5)	90.5
10. Did the participant ensure the blood has moved from the tube into the well?	126 (63.0)	74 (37.0)	63.0
11. Was the study participant able to pour 3 drops of buffer into the well?	182 (91.0)	18 (9.0)	91.0
12. Did the test fluid run across the strip?	185 (92.5)	15 (7.5)	92.5
13. Did the participant quit the process at any point?	3 (1.5)	197 (98.5)	98.5
14. Did the participant continue the process despite a missed or incorrect step?	187 (93.5)	13 (6.5)	93.5
Total usability index			**89.1**
Atomo2			
1. Did the study participant read/use the information sheet?	200 (100.0)	0 (0.0)	100.0
2. Was it difficult for the participant to remove the test device from the foil pouch?	1 (0.5)	199 (99.5)	99.5
3. Did the study participant massage finger for approximately 10 seconds to stimulate the blood flow?	166 (83.0)	34 (17.0)	83.0
4. Was the study participant able to twist the green sterility tab and pull it out?	200 (100.0)	0 (0.0)	100.0
5. Did the participant successfully push hard on the grey button to prick finger?	200 (100.0)	0 (0.0)	100.0
6. Was the study participant able to form a blood droplet by squeezing firmly behind the prick site?	197 (98.5)	3 (1.5)	98.5
7. Did the study participant successfully touch blood to channel?	197 (98.5)	3 (1.5)	98.5
8. Did the study participant adequately fill the channel with enough blood?	186 (93.0)	14 (7.0)	93.0
9. Did the participant successfully push hard on the button to activate the test?	198 (99.0)	2 (1.0)	99.0
10. Did the test fluid run across the strip?	199 (99.5)	1 (0.5)	99.5
11. Did the participant quit the process at any point?	0 (0.0)	200 (100.0)	100.0
12. Did the participant continue the process despite a missed or incorrect step?	200 (100.0)	0 (0.0)	100.0
Total usability index			**97.6**
Chembio			
1. Did the study participant read/use the information sheet?	198 (99.0)	2 (1.0)	99.0
2. Was it difficult for the participant to remove the test device from the foil pouch?	6 (3.0)	194 (97.0)	97.0
3. Did the study participant successfully place the stand on a flat surface?	199 (99.5)	1 (0.5)	99.5
4. Was the study participant able to carefully remove the buffer cap?	196 (98.0)	4 (2.0)	98.0

5. Did the participant correctly insert the buffer cap into the test stand?	196 (98.0)	4 (2.0)	98.0
6a. Was the study participant able to open the disinfectant wipe?	194 (97.0)	6 (3.0)	97.0
6b. Was the study participant able to open the sterile pad?	161 (80.5)	39 (19.5)	80.5
7. Did the participant swab finger with disinfectant wipe and allow to dry?	190 (95.0)	10 (5.0)	95.0
8a. Did the study participant successfully uncap safety lancet?	198 (99.0)	2 (1.0)	99.0
8b. Did the study participant successfully place red end of lancet against the side of fingertip?	198 (99.0)	2 (1.0)	99.0
9. Did the participant successfully press down firmly to prick their skin?	197 (98.5)	3 (1.5)	98.5
10. Did the study participant gently squeeze out the first blood drop?	198 (99.0)	2 (1.0)	99.0
11. Did the study participant use the sterile pad to wipe up the blood?	137 (68.5)	63 (31.5)	68.5
12. Did the study participant gently squeeze out second blood drop?	174 (87.0)	26 (13.0)	87.0
13. Was the study participant able to fill the testing device with an adequate amount of blood?	194 (97.0)	6 (3.0)	97.0
14a.Was the study participant able to insert tip of the device into the test stand opening?	194 (97.0)	6 (3.0)	97.0
14b.Was the study participant able to push firmly through the foil cap until 3 snaps were felt?	162 (81.0)	38 (19.0)	81.0
15.Did the participant check for pink stain formation within 1 minute of puncturing the buffer pot?	175 (87.5)	25 (12.5)	87.5
16.Did the participant quit the process at any point?	3 (1.5)	197 (98.5)	98.5
17.Did the participant continue the process despite a missed or incorrect step?	197 (98.5)	3 (1.5)	98.5
Total usability index			**93.7**
Orasure			
1. Did the participant read/use the IFU?	200 (100.0)	0 (0.0)	100.0
2. Was it difficult for the study participant to remove the test tube from the pouch?	20 (10.0)	180 (90.0)	90.0
3. Did the study participant remove the cap from the test tube?	196 (98.0)	4 (2.0)	98.0
4. Did the study participant have difficulty with sliding the test tube into the stand?	49 (24.5)	151 (75.5)	75.5
5. Was the study participant able to remove the test device from the pouch?	194 (97.0)	6 (3.0)	97.0
6. Did the study participant touch the flat pad?	27 (13.5)	173 (86.5)	86.5
7. Did the study participant collect the sample correctly?	152 (76.0)	48 (24.0)	76.0
8. Did the study participant place the test device in the test tube correctly?	198 (99.0)	2 (1.0)	99
9. Did the participant quit the process at any point? If Yes, explain	0 (0.0)	200 (100.0)	100
10. Did participant continue the process despite a missed or incorrect step?	200 (100.0)	0 (0.0)	100
Total usability index			**92.2**
Calypte			
1. Did the study participant read/use the information sheet?	200 (100.0)	0 (0.0)	100.0
2. Was it difficult for the participant to remove the test contents from the box?	3 (1.5)	197 (98.5)	98.5
3. Did the study participant have difficulty inserting the test tube into the box?	81 (40.5)	119 (59.5)	59.5
4. Did the study participant have difficulty with pulling the cap off the test tube?	24 (12.0)	176 (88.0)	88.0
5. Was the study participant able to remove the oral brush from the plastic bag?	200 (100.0)	0 (0.0)	100.0
6. Did the participant collect the sample correctly (brush 2x upper & 2x lower)?	194 (97.0)	6 (3.0)	97.0
7. Did the study participant insert the oral brush in the test tube correctly?	199 (99.5)	1 (0.5)	99.5
8. Did the study participant slowly push the oral brush up & down, inside the test tube correctly (6-8 X)?	195 (97.5)	5 (2.5)	97.5
9. Did participant squeeze fluid from the oral brush against the test tube correctly?	197 (98.5)	3 (1.5)	98.5
10. Did the study participant remove the oral brush from the test tube?	200 (100.0)	0 (0.0)	100.0
11. Did the study participant remove the test strip from the foil pouch correctly?	198 (99.0)	2 (1.0)	99.0
12. Did the study participant drop the test strip into the test rube correctly (arrows pointing down)?	198 (99.0)	2 (1.0)	99.0
13. Did the participant quit the process at any point?	0 (0.0)	200 (100.0)	100.0
14. Did the participant continue the process despite a missed or incorrect step?	200 (100.0)	0 (0.0)	100.0
Total usability index			**95.5**

n-number; %-percentage; IFU-information for use

Interpreting contrived results

Overall, participants could correctly interpret the non-reactive/negative (1346/1400 (96.1%); 91.0%-99.5%) and reactive/positive results (1357/1400 (97.0%); 94.5%-99.5%) accurately for each of the devices (Table 3). Weak reactive/positive results had a much lower number of total correct interpretations (1048/1400 (74.9%); 49.5%-94.0%) and most commonly, weak positive results were interpreted as non-reactive/negative. The invalid test result was read correctly in most cases (1290/1400 (92.1%) ;83.0%-98.0%).

Post HIVST

When asked what to do after testing positive, many of the participants (1358/1400 (97.0%); 92.0%-100.0%) stated that they would go to a clinic or seek treatment. For negative results, approximately half the participants (709/1400 (50.6%); 0.5%-82.5%) stated that they should re-test in the next three months, while just over one third (506/1400 (36.1%); 13.0%-69.0%) reported that they should condomize (Table 3).

Table 3. Contrived results, post-testing and user perceptions.

Outcomes	Biosure	INSTI (%)	Atomo1	Atomo2	Chembio	Orasure	Calypte	Total
Interpreting contrived results	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Non-reactive / Negative	186 (93.0)	198 (99)	199 (99.5)	195 (97.5)	188 (94.0)	182 (91.0)	198 (99.0)	1346 (96.1)
Reactive / Positive	189 (94.5)	199 (99.5)	198 (99.0)	191 (95.5)	191 (95.5)	192 (96)	197 (98.5)	1357 (97.0)
Weak reactive / Weak positive	149 (74.5)	188 (94.0)	173 (86.5)	173 (86.5)	126 (63.0)	99 (49.5)	140 (70.0)	1048 (74.9)
Invalid (no control line)	173 (86.5)	194 (97.0)	191 (95.5)	184 (92.0)	166 (83.0)	186 (93.0)	196 (98.0)	1290 (92.1)
What to do after HIVST								
If Negative/Non-Reactive								
Re-test in 3 months	59 (29.5)	162 (81.0)	162 (81.0)	60 (30.0)	1 (0.5)	100 (50.0)	165 (82.5)	709 (50.6)
Condomize	87 (43.5)	26 (13.0)	32 (16.0)	134 (67.0)	138 (69)	54 (27.0)	35 (17.5)	506 (36.1)
Other	54 (27.0)	12 (6.0)	6 (3.0)	6 (3.0)	61 (30.5)	46 (23.0)	0 (0.0)	185 (13.2)
If Positive/Reactive								
Visit clinic/seek treatment/counselling	189 (94.5)	198 (99.0)	199 (99.5)	195 (97.5)	193 (96.5)	184 (92.0)	200 (100.0)	1358 (97.0)
Other	11 (5.5)	2 (1.0)	1 (0.5)	5 (2.5)	7 (3.5)	16 (8.0)	0 (0.0)	42 (3.0)
Participant perceptions of HIVST process								
Were the Instructions for Use easy to understand?	186 (93.0)	198 (99.0)	197 (98.5)	199 (99.5)	196 (98.0)	198 (99.0)	196 (98.0)	1370 (97.9)
Was the device easy to use?	184 (92.0)	197 (98.5)	185 (92.5)	200 (100.0)	197 (98.5)	192 (96.0)	197 (98.5)	1352 (96.6)
Are you confident with performing this test on your own?	172 (86.0)	193 (96.5)	197 (98.5)	194 (97.0)	192 (96.0)	197 (98.5)	197 (98.5)	1342 (95.9)
Would you prefer to use this test at home? ((vs. get tested at a clinic)	162 (81.0)	160 (80.0)	162 (81.0)	166 (83.0)	159 (79.5)	167 (83.5)	155 (77.5)	1131 (80.1)
Will you use this test again?	193 (96.5)	172 (86.0)	194 (97.0)	192 (96.0)	193 (96.5)	200 (100.0)	200 (100.0)	1344 (96.0)
Will you recommend this test to a sexual partner/friend?	194 (97.0)	195 (97.5)	195 (97.5)	191 (95.5)	195 (97.5)	196 (98.0)	195 (97.5)	1361 (97.2)

n-number; %-percentage

Participant perceptions of the HIVST process

Nearly all of the participants found the device easy to use (1352/1400 (96.6%);92.0%-100.0%) and found the IFUs to be easy to understand (1370/1400(97.9%);93.0%-99.5%) (Table 3). Many participants (1342/1400(95.9%);86.0%-98.5%) felt confident using the device on their own and would prefer using the test at home instead of a clinic (1131/1400 (80.1%);77.5%-83.5%). Almost all participants (1344/1400 (96.0%);86.0%-100.0%) would use the test again and (1361/1400 (97.2%);95.5%-95.5%) would recommend the test to a partner or friend.

Participants acknowledged difficulty with some steps due to kit engineering (e.g. difficulty assembling the device, or fitting parts together), particularly where there was a tight fit or firm pressure was required. Participants made suggestions where some issues could be resolved by the IFU–asking for some steps to be clarified or emphasized in places:

> *"Some steps were hard to follow, pictures help"*
>
> - Male, 25 years old, FS

When asked what they liked least about their HIV self-test, participants in the FS studies identified a general dislike of the needle, however this was reported by less than 12% (6%-11%) of the fingerstick participants. Many participants had never used a safety lancet and were nervous about the needle, but then expressed surprise that it wasn't as painful as anticipated. Some participants expressed frustration with the fingerstick process ("needle not working" and "needle not sharp enough") and could not acquire enough sample (particularly noted for device Atomo1). For the fingerstick step, participants suggested improved instruction to successfully apply the lancet ("press firmly" with a picture of the correct location) and to obtain the necessary sample volume ("keep squeezing" to form blood droplet):

> *"Safety lancet is bit confusing; the producer should make it more visible."*
>
> - Male, 48 years old, FS

For the OF studies, participants had minimal apprehension about obtaining a specimen; most of the complaints focused on difficulties with assembling the kit components ("cap is too tight" and "where to insert the tube"). When asked what they liked best about their HIV self-test, both OF and FS participants overwhelmingly liked the convenience and confidentiality of a self-test. Approximately 7% of OF self-testers specifically stated that that they like that their test required "no needle" and "no blood" (though four OF participants stated a higher confidence for blood-based testing).

Both OF and FS participants preferred home-based self-testing to clinic-based testing, and appreciated that the HIV self-test was confidential, fast, did not require clinic queues and gave them autonomy for their health decisions.

> *"Home test is easier and less scary compared to clinic."*
> - Male, 30 years old, OF

Several participants expressed a desire for a trained professional to be available to assist in using the device (both FS and OF), if necessary, while others were concerned about the lack of counselling available with the HIVST.

> *"Before the client buy this product, the must be someone to demonstrate to the clients at pharmacy on how to use this product."*
> - Male, 19 years old, OF

> *"Where there is no counselling wrong decisions can be made."*
> - Male, 30 years old, FS

Discussion

While this is the first large-scale usability study incorporating multiple HIVSTS in South Africa, the strong usability outcomes, are consistent with recent studies conducted in other populations. A study of the Exacto Test HIV in the Central African Republic showed that 91% of participants found the test easy to use and 91.6% performed the test correctly, however 23% asked for oral assistance [28]. Similarly, a Kenyan INSTI usability study showed that 94.3% of participants found the test easy to use [23]. The high average usability index of 93.8% is further corroborated by 96.6% of all participants stating that the HIVSTs were easy to use.

Despite the high usability scores, this evaluation also provided observations and perspectives that may improve upon current offerings by identifying points of confusion or hesitation, as well as any critical and non-critical errors made during the self-testing process. For each device, difficulties with packaging, instructions, and/or kit components were identified for improvement to increase ease-of-use and reduce misuse of the self-test. Each device manufacturer received a final usability report to help assess product readiness for the HIV self-testing market in South Africa, along with recommendations for any HIVST kit improvements.

User errors were high when participants had difficulty obtaining and transferring the specimen. For the FS devices, the most common specimen collection errors included lancing mistakes, not acquiring a sufficient blood droplet, or not adequately filling the transfer capillary. These results

were comparable to a previous usability study of Atomo1 in adolescents from Cape Town, South Africa [21]. Errors in FS sample acquisition might be decreased through improvements to the IFU and/or more reliable lancets. For the OF devices, the most common specimen collection errors came from incorrectly swabbing the mouth, which could also be decreased through improvements to the IFU. Since no diagnostic results were collected, these user errors cannot be directly linked to incomplete or incorrect test results; follow-on studies of full diagnostic performance are currently underway.

As participant responses suggest, it would be beneficial to have a choice between whole blood or oral fluid HIVST device, as different users have indicated a preference for both; one kind of self-test modality is unlikely to suit everyone. This variance was also observed in a recent study of men who have sex with men (MSM) in Mpumalanga, South Africa, which showed that OF tests (OraSure) were easier to use, while the FS tests (Atomo) were preferred by participants [29]. Even with the choice of OF and FS devices, self-testing alone, is unlikely to be beneficial for everyone who needs an HIV screening test, as roughly 20% of all participants indicated they were uncomfortable performing the test without guidance or counselling at hand. This proportion was similar across 7 devices, suggesting that people's views on this are unrelated to any technical aspect of HIVST devices and may instead indicate a social preference. Similar findings were published in an OraQuik study from Singapore, which suggested that the acceptability of HIVSTs may be influenced by socioeconomic status [30]. Age may also play a factor, as the Cape Town adolescent usability study showed slightly lower usability scores with a similar style data collection tool, as participants scored the device 4 out of a maximum rating of five [21]. A multi-dimensional approach including home-testing, community-supported testing and clinic- based testing will likely be needed to reach key and under-tested populations, including men, adolescents and serodiscordant partners. The ability to privately and easily perform an HIV self-test is a much-needed innovation to enable earlier diagnosis of HIV and empower individuals to monitor their own health and behaviour.

Although not part of the usability index, the interpretation of contrived results and what to do after testing also identified some areas of possible improvement. While most participants correctly interpreted non-reactive/negative, reactive/positive and invalid (no control line) results, one quarter of all participants misinterpreted the weak reactive/positive, most commonly as non- reactive/negative. The results for the positive, negative and invalid tests were similar to the Central African Public study, however that study did not investigate the interpretation of weak positive results [28]. The contrived weak positive results ranged in intensity and were specific to each product, so some device weak results may have appeared feint or lighter than others. Most of the IFUs provided simple recommendations for test results with the pictured examples, such as "go to clinic" for a reactive/positive result, and "re-test in 3

months" for a non-reactive/negative result, however some IFUs did not include recommendations for the non- reactive/negative or invalid test results. We noted that participants achieved the most accurate result interpretation when the test device could be placed next to "life sized" examples of the possible test outcomes in the IFU. In order to achieve the most accurate result interpretation, "life sized" comparison examples of all possible test outcomes should be prominently displayed in the IFUs of each HIVST, a suggestion that was also made by Bwana et al in the Kenyan study, as that IFU also lacked a weak positive image [23]. This should also be coupled with simple IFU recommendations of what to do after testing, in the case of each possible result.

The results of the HSTAR001 Usability study presents general guidelines for safe and easy-to-use HIVST test kits including minimizing packaging and clearly marking kit components, simplifying and ordering IFU steps (placing particular emphasis on key steps where necessary), minimizing the number of words used in favour of simple pictures and universal icons (e.g. for the FS have a picture of the target (finger) and orientation of lancet, emphasizing the need to press firmly and for oral fluid to include a picture how the user must place or move tool inside their mouth), providing interpretation of all test outcomes and including "life size" pictures for device comparison, and clearly indicating the next steps for each type of test outcome.

Limitations

This study presented some limitations. The convenience sampling may present a selection bias, as there were different proportions of sub-demographics between devices, which may have been due to the different communities surrounding each study location. The evaluation of the devices in series ensured no cross-contamination, however the participants from the community may have become more aware of HIVST by the time the last device was tested. For data collection, there is no validated or standardized usability test for HIVSTs, so the product-specific semi-structured questionnaire was developed internally and used to quantify usability. This questionnaire only allowed for each device to be evaluated independently. No direct comparisons between products could be made, as a result of different device components and IFUs not being standardized across kits. For example, there was no universal standard for intensity of a weak positive used to test readings of contrived results. The WHO prequalification only requires independent data on usability and does not require any direct comparisons between products, however we are working on developing a more standardized tool as a separate project as comparisons would be beneficial as more HIV self-tests reach the market.

The usability and comprehension of test instructions are also likely to be context and population specific (for instance, high levels of participants preferring English IFUs), limiting the generalisability of these findings. Some responses may have been influenced by participants'

prior HIV testing experience and post-test counselling prior to this study, which is high in the sampling area. Since no diagnostic results were collected, we could not ascertain whether the user errors identified in the study led to incomplete or incorrect test results in this usability study; follow-on studies of full diagnostic performance are currently underway.

Conclusions

The results of the HSTAR001 HIVST Usability studies indicate that several devices show overall high levels of usability (ease-of- use) and acceptability in the hands of lay people. Correlating these usability results to test outcome and diagnostic accuracy is the next step in forthcoming studies.

Each of these 7 HIVST devices evaluated in this study is intended to enter the South African HIVST market–and more are likely to follow. Several HIVST candidates are close to final evaluation of test performance and international regulatory approval, and one has recently achieved approval from the WHO PQ (Orasure). Lessons learnt from this evaluation have resulted in guidelines for use, which if taken up by manufacturers will assist in their HIVST candidates achieving WHO PQ Test design, usability and performance, however, are only the first step; to pave the way for HIVST uptake, there needs to be policy engagement to approve and support distribution channels appropriate to both the private pharmacy-based and public health markets.

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Supporting information

S1 Data Collection Checklists[9]– a file titled *S1_Checklists.pdf* has been uploaded to the Data Package file

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Competing interests

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CHAPTER 3. Performance assessment of four HIV self-test devices in South Africa: A cross-sectional study

This chapter is based on:

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Abstract

HIV self-testing (HIVST) has been introduced to supplement existing HIV testing methods to increase the number of people knowing their HIV status. Various HIVST kits have been developed; however, in many countries, their entry into the market is contingent on either being listed as World Health Organization (WHO) prequalified diagnostics/products or being approved by that country's health device regulator or both. In this cross-sectional study, we evaluated the usability, sensitivity and specificity of HIVSTs, as directed by the WHO prequalification literature. A boxed, sealed HIVST kit was provided to enrolled lay users with no further instruction, who then performed the test under observation. For each HIVST, a product-specific semi-structured checklist was used to calculate a usability index, while the sensitivity and specificity of each HIVST were calculated by comparing the HIVST results to the 'gold standard' – fourth-generation ELISA laboratory blood test. The average usability index was 97.1% (95.9–97.8%), while the average sensitivity and specificity were 98.2% (96.8–99.3%) and 99.8% (99.4–100.0%), respectively. We also diagnosed 507 (15.1%) HIV-positive participants from the general population. The average usability index, sensitivity and specificity were all comparatively high, and these results corroborate previous usability and performance studies from other regions. These results suggest HIVSTs are appropriate for the South African market and can assist manufacturers with readying their devices for final WHO prequalification evaluation.

Significance

- This study has followed the WHO Technical Specification Series for the prequalification of HIV self-test devices, so the usability, sensitivity and specificity results may be used to inform the WHO prequalification process.
- The average usability index (97.1%), sensitivity (98.2%) and specificity (99.8%) were all very high, and these results support previous usability and performance studies from other regions, which suggest HIV self-tests are appropriate for WHO prequalification, and subsequently, the South African market.
- This study also diagnosed 507 (15.1%) HIV-positive participants from the general population – slightly higher than the national prevalence of 13.1%.

Introduction

The UNAIDS and the World Health Organisation (WHO) 90–90–90 strategy released in 2015 has been adopted globally [1]. Despite significant progress made towards improving HIV testing rates in South Africa using the conventional, facility-based approach, it was still insufficient to reach the goal of testing 90% by 2020 [2]. Inclusion of HIV self-testing (HIVST) in the South African strategy was considered to complement (by promoting use in populations who do not usually exhibit facility-based health seeking behavior) and supplement (by providing a different option for HIV testing) existing methods while possibly improving HIV testing uptake thereby facilitating target attainment [3,4].

HIVST involves self-sampling of the user's oral fluid or blood specimen (dependent on the kit requirement), performing the HIV rapid diagnostic test (RDT), and then interpreting the result. The HIVST kits are intended to be used in a private setting, by a general population that encompasses a broad range of ages, education and literacy levels and nationalities. The benefit of HIVST includes immediate and confidential test results, and may encourage testing by groups who may otherwise avoid testing due to stigma, or the time and effort required for a clinic visit. HIVST can also promote more frequent testing, enable earlier diagnosis of HIV, may modify risk behaviours and may empower people to become more proactive and engaged in their healthcare decisions [5-7].

The first HIVST RDT approved for home use by the Food and Drug Administration (FDA) in the United States was OraQuick ADVANCE Rapid HIV-1/2 Antibody Test in 2012 [8] and since then, studies have continued to show the benefits of HIVST across several populations [9-12]. Based on this growing body of evidence, the WHO released guidelines for HIVST use in 2016, and strongly recommends HIVST as a way to supplement existing HIV testing services [13]. These guidelines recommend that only validated, WHO Pre-qualified products should be used in public health programmes, and this position has also been adopted by the South African National Department of Health in their *National HIV Self Screening Guidelines 2018* [14].

In order to validate products, the World Health Organization (WHO) Prequalification (PQ) of In Vitro Diagnostics (IVDs) coordinated through the Department of Essential Medicines and Health Products (EMP) WHO PQ has begun a prequalification process for HIVST to identify products which follow the best practices and standards set by international groups, including the International Medical Devices Regulatory Forum, the Global Harmonization Task Force, the United States FDA and the European Regulatory Authorities [15]. In December 2017, the WHO released its Technical Specification Series for the PQ process for HIV Self-Test devices. The WHO PQ process includes a review of the device packaging, instructions for use, analytical and clinical performance data, as well as a manufacturing site inspection. Device manufacturers must also

demonstrate that self-testing is supported by evidence from studies that explore usability and clinical performance, among a broad population of untrained intended users [15].

The HIV Self-Testing Assessments and Research (HSTAR) programme at the Wits Reproductive Health and HIV Institute (Wits RHI) is a Bill and Melinda Gates Foundation-funded programme to support HIVST developers looking to submit their device for prequalification and those seeking to enter the South African market, by independently providing data on HIVST usability (HSTAR001) and usability, performance and accuracy (HSTAR003) in the hands of untrained users.

The usability testing of seven prospective HIVST devices was recently completed with contrived results, as part of the HSTAR001 trial in Johannesburg, South Africa and the usability index for each device was high, ranging from 84.2-97.6% [16]. Following a similar methodology, this study (HSTAR003) aimed to build onto those results, and inform the WHO PQ process by evaluating the usability of four HIVST candidates in clinical practice, with real-time results, instead of contrived ones. Additionally, the clinical performance and accuracy of these HIVSTs was investigated using sensitivity and specificity, by comparing results with the laboratory 4th generation ELISA as the gold standard.

Methods

Study Design

This cross-sectional study was implemented from March 2017 until November 2018, using the WHO PQ published guidance. The HIVST devices were evaluated independently of the manufacturers and in series, to ensure no cross-contamination of assessments. To prevent participants from enrolling for more than one device, a fingerprint scanning Biometric Enrolment System, was used.

HIVSTs

Four HIVST devices were assessed: three fingerstick whole blood (FS) devices and one oral fluid (OF) device. The three FS devices were produced by Biosure Ltd (United Kingdom), Biolytical Laboratories (INSTI) (Canada) and Chembio Diagnostic Systems (USA), while the OF test was produced by Orasure Technologies (USA). Each HIVST device included the manufacturer's instructions for use (IFU) and other kit components, which were presented as intended for sale or distribution in South Africa. No additional job aids, demonstration or assistance was provided other than manufacturer packaged materials.

Study Participants

Convenience sampling was used to recruit adult participants from Wits RHI clinical trial sites in the inner city of Johannesburg. Included volunteers had to be at least 18 years old, could read

English and were first-time HIV self-testers with a self-reported unknown HIV status. Individuals were excluded if they had any prior experience with HIV self-testing or were health workers and lay counsellors who had performed HIV testing. Also excluded were participants who had received an experimental HIV vaccine or were taking HIV pre-exposure prophylaxis, persons known to be HIV positive or had any extenuating condition (such as intoxication or acute sickness) which would interfere with the process [16].

Using the WHO Prequalification Technical Specification Series document for guidance, a blended sample size of 900 participants was required for the usability assessment of each device. This sampling intended to blend high and low-risk populations, and during training recruiters were made conscious to recruit equal gender participation, diverse age groupings and education levels [15].

Field Procedures

All study procedures were conducted by a team of Good Clinical Practice trained researchers, and the self-testing followed the same procedures as HSTAR001 [16] in that participants were handed a sealed test kit and they were provided with no further information about the device or test procedure. They were then requested to perform the test while being silently observed. The observer documented the process using a product-specific questionnaire. This was followed by a post-test interview.

Instead of being handed a contrived result to interpret, the participants' real self-test result was noted by the participant, then independently read and confirmed by a research nurse. In order to evaluate the performance and accuracy of the HIVST results, a 5mL blood sample was drawn at the conclusion of each self-test, and a 4^{th} generation laboratory ELISA test (ABBOTT Laboratories, Chicago, USA) was performed within 24 hours at the Wits Clinical Laboratory Services (a South African National Accreditation System (SANAS) approved, Good Clinical Laboratory Practice-compliant facility). The ELISA laboratory test was used as the gold standard for the calculation of clinical sensitivity and specificity for each HIVST device.

HIV status was subsequently determined on-site for all participants, irrespective of HIV status on the HIVST, using nurse-administered professional tests following the South African National Confirmatory Testing Algorithm [14]. Fingerstick samples were obtained using the Advanced Quality™ Rapid Anti-HIV 1&2 Test (RDT1) and the Abon™ HIV 1/2/O Tri-Line Human Immunodeficiency Virus Rapid Test Device (RDT2). If both the HIVST and RDT1 indicated a non-reactive/negative result, the participant was diagnosed as HIV negative. If one or both tests were reactive/positive, then the RDT2 test was performed. If both professional tests (RDT1, RDT2) were negative, then the participant was diagnosed as HIV negative. If both professional tests

(RDT1, RDT2) were positive, then the participant was diagnosed as HIV positive and provided with a medical referral. In cases of discordant professional test results, the ELISA test was used for final diagnosis, and the participant was referred to a clinical site for the test results and follow-up.

Data Collection

For the recently completed HSTAR001 usability assessment the WHO prequalification literature was used to design, pilot test and implement a product-specific semi-structured questionnaire for data collection [16] and this was also used in the current HSTAR003 study. The usability questionnaire comprised of a HIVST process checklist guided by IFU steps, used to calculate usability index and a post-test interview that investigated the participants' competency, experiences and recommendations. For performance and accuracy evaluations, the ELISA laboratory test results were provided back to the research staff as an electronic copy within 24 hours via email, and a hard copy hand delivered within seven days.

Data Analysis

After data collection, field workers transcribed the questionnaire results into an Excel database. Quantitative data was analyzed with descriptive statistics. Each batch of test kits went through a quality control check and 10% of all data entries were also checked by administrators for quality control.

To measure the performance and accuracy of each HIVST, sensitivity and specificity were analyzed. Sensitivity refers to the ability of the HIVSTs to accurately detect truly positive tests, while specificity refers to the ability of the HIVSTs to correctly filter out truly negative test results. Both outcomes improve as they approach 100%, and their calculations are presented in Figure 1. The data supporting the results of this study are available upon request to the corresponding author.

Ethical Considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (No. 161110). All participants signed an informed consent form and participants received a reimbursement for their participation. The manufacturer played no part in the study design, procedures or analysis of findings.

Sensitivity = [TP / (TP + FN)] x 100, where

- TP (true positive) is positive HIVST results, in agreement with positive ELISA laboratory results, and;
- FN (false negative) is negative HIVST results, discordant with positive ELISA laboratory results.

Specificity = [TN / (TN + FP)] x100, where

- TN (true negative) is negative HIVST results, in agreement with negative ELISA laboratory results, and;
- FP (false positive) is positive HIVST results, discordant with negative ELISA laboratory results.

Figure 1: Sensitivity and specificity calculations.

Results

Demographics

Table 1 presents the demographic data for each of the HIVSTs and there was a diverse distribution of age groupings and education levels. The majority of participants were South Africans (3201/3600; 88.9%) under 35 years of age (2842/3600; 78.9%) and just over half of them (1944/3600; 54.0%) were male. The majority of participant's had graduated secondary school (2056/3600; 57.1%) or attended tertiary school (1428/3600; 39.7%) while only 116/3600; 3.2%) had primary school or less. Only 853 (23.7%) were employed, while 2279 (63.3%) were unemployed and 467 (13.0%) were students.

Usability assessment

The four HIVSTs had an average of usability index of 97.1% (95.9%-98.8%) on their product-specific usability assessment (Table 2). The full usability indexes for each HIVST are available in Supplementary table 1. Despite the high usability, there were several spoiled tests (233/3600; 6.5%), in which critical errors prevented the test from producing a valid result. The majority of spoiled tests came from specimen collection errors (101/3600; 2.8%) or process errors (160/3600; 4.4%). A small number of spoiled tests were due to participants asking for assistance (7/3600 (0.2%) or quitting (12/3600; 0.3%). Four (0.1%) participant results were also deemed invalid due to defective kits, as they did not present a positive internal control line, even though the participants correctly completed all steps.

Table 1: Participant demographics

Demographic	Biosure	Orasure	INSTI	Chembio	Total
	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
Sample size	900 (100.0)	900 (100.0)	900 (100.0)	900 (100.0)	3600
Age					
18-25 years old	418 (46.4)	339 (37.7)	501 (55.7)	425 (47.2)	1683 (46.8)
26-35 years old	292 (32.4)	326 (36.2)	255 (28.3)	286 (31.8)	1159 (32.2)
Over 35 years old	190 (21.2)	235 (26.1)	144 (16.0)	189 (21.0)	758 (21.1)
Sex					
Female	419 (46.6)	383 (42.6)	460 (51.1)	394 (43.8)	1656 (46.0)
Male	481 (53.4)	517 (57.4)	440 (48.9)	506 (56.2)	1944 (54.0)
Nationality					
South African	820 (91.1)	745 (82.8)	829 (92.1)	807 (89.7)	3201 (88.9)
Zimbabwean	76 (8.5)	117 (13.0)	52 (5.8)	78 (8.7)	323 (9.0)
Other	4 (0.4)	38 (4.2)	19 (2.1)	15 (1.6)	76 (2.1)
Education Level					
Primary School or	30 (3.3)	35 (3.9)	18 (2.0)	33 (3.7)	116 (3.2)
Secondary School	543 (60.3)	561 (62.3)	404 (44.9)	548 (60.9)	2056 (57.1)
Tertiary School (any)	327 (36.4)	304 (33.8)	478 (53.1)	319 (35.4)	1428 (39.7)
Employment Status					
Employed	211 (23.4)	208 (23.1)	149 (16.6)	285 (31.7)	853 (23.7)
Unemployed	581 (64.6)	618 (68.7)	647 (71.9)	433 (48.1)	2279 (63.3)
Student	107 (11.9)	74 (8.2)	104 (11.5)	182 (20.2)	467 (13.0)
Didn't disclose	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Abbreviations: Freq- frequency; %-percentage

The process and collection errors that limited usability were specific to each device. Common errors across most FS devices were due to incorrect lancing technique or lancet placement, resulting in insufficient blood available, failure to transfer the blood specimen to the device or buffer, and failure to apply the correct volume of buffer. For the OF test, the most common errors were incorrect sampling technique during swabbing of the gum, and not transferring the device into the buffer solution.

Biosure and Chembio had the most spoiled tests. The Chembio and Biosure products use identical kit components and follow the same principle of testing however the kit components are packaged differently and have a different IFU design to align with Chembio and Biosure branding. The most common error seen across both products was related to the step: "Push hard through the foil cap until fully seated in the buffer cap." Those that made errors with this step had not pushed hard through the foil cap, and only inserted the tip of the device into buffer which resulted in an inactive test and invalid result (no lines on test strip).

Table 2: HIVST usability and performance outcomes.

Usability	Biosure (n=900)	Orasure (n=900)	INSTI (n=900)	Chembio (n=900)	Total (n=3600)
	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
Spoiled tests					
Invalid Device	0 (0)	0 (0)	3 (0.3)	1 (0.1)	4 (0.1)
Required assistance	0 (0)	7 (0.8)	0 (0)	0 (0.0)	7 (0.2)
Quit	6 (0.7)	3 (0.3)	3 (0.3)	0 (0.0)	12 (0.3)
Collection error	36 (4.0)	7 (0.8)	31 (3.4)	27 (3.0)	101 (2.8)
Process error	60 (6.7)	11 (1.2)	15 (1.7)	74 (8.2)	160 (4.4)
Total	84 (9.3)	23 (2.6)	51 (5.7)	75 (8.3)	233 (6.5)
Successful HIVSTs	816 (90.7)	877 (98.2)	849 (94.3)	825 (91.7)	3367 (93.5)
Performance	Biosure (n=816)	Orasure (n=877)	INSTI (n=849)	Chembio (n=825)	Total (n=3367)
	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
True Positive	126 (15.4)	152 (18.6)	98 (11.5)	122 (14.8)	498 (14.8)
True Negative	687 (84.2)	717 (87.9)	750 (88.3)	699 (84.7)	2853 (84.7)
False Positive	0 (0.0)	7 (0.9)	0 (0.0)	0 (0.0)	7 (0.2)
False Negative	3 (0.4)	1 (0.1)	1[a] (0.1)	4 (0.5)	9 (0.3)
Outcomes	Biosure (n=816)	Orasure (n=877)	INSTI (n=849)	Chembio (n=825)	Total (n=3367)
	(%)	(%)	(%)	(%)	(%)
Usability Index	95.9	97.4	97.1	97.8	97.1[b]
HIVST sensitivity	97.7	99.3	99.0	96.8	98.2[c]
HIVST specificity	100.0	99.4	100.0	100.0	99.8[c]

Abbreviations: Freq- frequency; %-percentage

[a] one indeterminate ELISA result excluded, unable to recall participant for re-testing. Participant was conditionally diagnosed as HIV negative, as all three rapid tests (HIVST and both professional tests were negative).

[b] usability was product specific, so direct comparisons between products should not be inferred

[c] Total sensitivity and selectivity calculation with total TP, TN, FP and FN, not averages.

Performance assessment

Only participants who successfully achieved a self-test result on their own (3367/3600 (93.5%); range: 816/900 (90.7%) to 877/900 (98.2%)) were included in the performance calculation for clinical sensitivity and specificity; any incomplete tests or quits were not used to calculate the device performance. In total, there were 498 (14.8%) true positive HIVSTs (positive for both HIVST and ELISA), seven (0.2%) false positive HIVSTs (positive for HIVST, negative for ELISA) 2853 (84.7%) true negative HIVSTs (negative for both HIVST and ELISA) and nine (0.3%) false negatives (negative for HIVST, positive for ELISA). This resulted in an average sensitivity of 98.2% and a specificity of 99.8%, while also diagnosing 507 (15.1%) HIV positive (sum of the true positives and false negatives) participants from the general population. The individual HIVST results are presented in Table 2.

Discussion

While previous studies have evaluated the usability of HIVSTs with contrived results, this is the first South African report on the clinical performance of multiple devices with real-time results interpretation. The results of this study add to the growing body of evidence that supports the use of HIVSTs as a user-friendly and accurate testing approach to reach populations that may not have access to traditional clinic-based testing. A 2018 systematic review assessed the reliability of HIVSTs from 20 reports across 16 studies conducted between 1995-2016. In this review, 16 (80%) had a specificity greater than 98%, and although sensitivity varied substantially, 18 (90%) of the reports had a sensitivity greater than 80% [17]. Furthermore, an Orasure study from Singapore in 2012 (n=994) achieved a similar sensitivity of 97.4% and a specificity of 99.9% [18]. Another recent study of INSTI in Kenya (n=354) also revealed comparable results to our study with a sensitivity of 98.99% and a specificity of 98.15% [19]. Three hundred and thirty (94.29%) participants found the device was easy to use, and the 15.1% of participants that tested positive in this study was slightly higher than the national prevalence of 13.1% [20].

While corroborating previous results [16-19], this South African study demonstrates the sensitivity and specificity values of four HIVSTs, to be higher than those attained during performance measurement for FDA approval [21], with a substantial sample size as outlined in the requirement for WHO prequalification. The National Department of Health in South Africa requires that any HIVST it procures or is used on their sites must be approved by the South African Health Products Regulatory Authority (SAHPRA) or be prequalified by the WHO.

The high sensitivity and specificity of each HIVST evaluated in this study suggested that they should all be considered for approval, as they also meet all of the other standards outlined by the WHO prequalification documents. Each batch of devices were manufactured under ISO 14385 standards required for the design and manufacture of medical devices and each HIVST included

IFUs with minimal language and simple pictorial instructions. At the time of this publication submission, two of the four devices in this assessment, OraSure and INSTI, had been prequalified by the WHO using data generated in this study [22]. Subsequent to this study Chembio also received prequalification. Data from these studies have been separately shared with SAHPRA, the SA National Department of Health and the South African National Institute for Communicable Diseases in order to facilitate the approval and usage of the product in implementation programs such as the Self-Test Africa (STAR) project.

Despite the high levels of sensitivity and specificity, there was a number of user errors (notably Biosure and Chembio), highlighting areas for improvement. Refining and tailoring the IFU to target markets (an action consequently implemented by Biosure and Chembio) and simplifying the device design could increase the overall usability of the device, further minimizing errors. Whilst errors are expected in the hands of untrained users, it is imperative that users are able to recognize that an error has been made, and that the test invalidates itself, i.e. no control line/dot appears when a critical error is made. Tests which do not have specimen control lines, and produce control lines in the absence of any human specimen can prove to be detrimental to HIVST as it could lead to an increase in false negative results. In order to build from these results and create a more robust body of evidence, future testing should be conducted with, and opinions elicited from, more diverse groups that include wider demographics and participants that are recruited independent of a clinical setting.

Limitations

This study has several limitations. A selection bias may have been created with convenience sampling, and while the evaluation of the devices in series ensured no cross-contamination, the general population may have become more aware of HIVST by the time the last device was tested, due to limited but expanding media coverage. The readability and comprehension of test instructions (we only used English IFUs for this evaluation) may be context and population specific, which limits the generalisation of these findings. Furthermore, an observation bias may be present, as the study was conducted under observation in a clinical setting, instead of alone in their homes.

Similar to the limitations of the HSTAR001 usability study, there is no validated or standardized usability test for HIVSTs, so the product-specific semi-structured questionnaire from HSTAR001 was used to quantify usability [16]. No direct comparisons could be made because of the different device components and non-standardized IFUs across kits. The sensitivity and specificity of each test also do not allow for direct comparisons, as these results were independently benchmarked against a gold standard, and not each other.

A fifth HIVST, Atomo, withdrew from the study after halfway through data collection, so these results were not included in the aggregated data, or explored in the discussion, however, the manufacturer did independently receive WHO prequalification for the device in the period post withdrawing from the study [23].

Conclusions

The four devices that were fully evaluated in this study and performed well, are among a growing number of HIVSTs that intend to enter the South African market; OraSure, Chembio and INSTI have already received their WHO prequalification [24] and Biosure also received approval for use in South Africa. The results of this HSTAR003 performance evaluation methodology may also be used to guide similar evaluations among different populations. In the coming years, various HIVSTs will gain approval and enter the marketplace, which means that policies and distribution channels must be appropriately developed to accommodate this influx.

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CHAPTER 4. Improving Linkage to and Retention in Care in Newly Diagnosed HIV-Positive Patients Using Smartphones in South Africa: Randomized Controlled Trial

This chapter is based on:

Venter WDF, Fischer A, Lalla-Edward ST, Coleman J, Lau Chan V, Shubber Z, Phatsoane M, Gorgens M, Stewart-Isherwood L, Carmona S, Fraser-Hurt N. Improving Linkage to and Retention in Care in Newly Diagnosed HIV-Positive Patients Using Smartphones in South Africa: Randomized Controlled Trial. *JMIR Mhealth Uhealth* 2019;7(4):e12652

Author contributions: **Venter WDF:** Conceptualization (lead), Methodology (equal), Writing-Reviewing and Editing, Data curation (supporting), Funding acquisition. **Fischer AE:** Data curation (lead), Methodology (equal), Formal analysis (lead), Writing- Original draft preparation. **Lalla-Edward ST:** Formal Analysis (supporting). **Coleman J:** Investigation (lead). **Lau Chan V:** Investigation (lead). **Shubber Z:** Investigation (supporting), Software (supporting). **Phatsoane M:** Investigation (supporting). **Gorgens M:** Funding acquisition, Supervision (supporting). **Stewart-Isherwood L:** Conceptualization (supporting). **Carmona S:** Methodology, Resources. **Fraser-Hurt N:** Supervision (lead), Software (lead), Project administration.

Abstract

Background

South Africa provides free antiretroviral therapy for almost 5 million people living with HIV, but only 71% of the eligible people are on treatment, representing a shortfall in the care cascade, especially among men and youth. Many developing countries have expanded access to smartphones; success in health apps raises the possibility of improving this cascade.

Objective

SmartLink is a health app for Android smartphones providing HIV-related laboratory results, information, support, and appointment reminders to engage and link patients to care. This study aimed to evaluate the ability of SmartLink to improve linkage to care for HIV-positive smartphone owners.

Methods

This study was a multisite randomized controlled trial in Johannesburg. The intervention arm received the app (along with referral to a treatment site) and the control arm received the standard of care (referral alone). Linkage to care was confirmed by an HIV-related blood test reported on the National Health Laboratory Service database between 2 weeks and 8 months after initiation.

Results

A total of 345 participants were recruited into the study; 64.9% (224/345) of the participants were female and 44.1% (152/345) were aged less than 30 years. In addition, 46.7% (161/345) were employed full time, 95.9% (331/345) had at least secondary school education, and 35.9% (124/345) were from Zimbabwe. Linkage to care between 2 weeks and 8 months was 48.6% (88/181) in the intervention arm versus 45.1% (74/164) in the control (P=.52) and increased to 64.1% (116/181) and 61.0% (100/164) (P=.55), respectively, after the initial 8-month period. Moreover, youth aged 18 to 30-years showed a statistically significant 20% increase in linkage to care for the intervention group.

Conclusions

Youth aged less than 30 years have been historically difficult to reach with traditional interventions, and the SmartLink app provides a proof of concept that this population reacts to mobile health interventions that engage patients in HIV care.

Introduction

Background

South Africa has the largest antiretroviral therapy (ART) program in the world, which provides free ART to approximately 4.4 million people living with HIV [1], and since its introduction in 2004, AIDS-related deaths and new HIV infections have been reduced by 58% and 46%, respectively [1]. The country strategy has been created in line with international guidelines and updated with the emergence of new bodies of evidence and global initiatives [2-4].

In 2015, the *90-90-90* initiative was introduced by the Joint United Nations Programme on HIV/AIDS and the World Health Organization as a way to further decrease new infections among the population, recognizing the large impact of ART on infectiousness, while also optimizing individual health. The initiative maximizes the effect of ART coverage by emphasizing that 90% of HIV-positive people should know their status, 90% of those eligible for ART should be initiated on ART, and 90% of those on ART should achieve and maintain viral suppression [5].

South Africa has accomplished moderate success with HIV testing and viral suppression, achieving 85% and 86% success rates, respectively; however, only 71% of the people eligible for ART are on treatment [6]. It is well documented that patients, especially young people aged less than 30 years and men, are being lost to follow-up along the entire HIV care cascade, but the most significant attrition is found during the stage from HIV diagnosis to the start of treatment [7-9]. Improving this deficit is needed to ensure that patients are initiated on ART early as patients lost during linkage to care often return as late presenters when they become seriously ill. Late presenters may also continue spreading the virus, further increasing the risk of infection and threatening the 90-90-90 targets [10].

In September 2016, South Africa adopted the *treat all* approach for ART treatment by dropping the CD4 thresholds for ART initiation completely [11], yet patients could still expect several clinic visits before initiating ART [12]. These visits consist of initial HIV testing, followed by determination of treatment eligibility, adherence counseling, and education, as well as baseline blood tests and a physical examination before receiving the antiretrovirals [12]. Each of these visits represents a risk to the continuum of care of the newly diagnosed HIV cases, and simplifying this process has been hypothesized as a way to decrease patient drop-off. Various interventions such as home-based testing and treatment and same-day initiation of ART have been tested to address this attrition, but there remains a gap [10,12-14].

The emergence of mobile health (mHealth) in developing countries has enabled some successful interventions across the continuum of HIV care, especially on the promotion of treatment adherence. With 90% of the world's population living in areas with mobile phone coverage and two-thirds of these people able to access data on their devices, mHealth provides an efficient

method to engage the population [15]. Short message service (SMS) messages and mobile apps have been used with moderate success in developing countries to improve ART adherence and appointment attendance [16-19]. South Africa has also experienced success with mHealth interventions, including the MomConnect program, which provides antenatal support through SMS and a help desk to almost 2 million pregnant mothers across the country [20].

The majority of mHealth interventions still focus on SMS text messaging, but by 2020, smartphone penetration in South Africa is expected to exceed 50% of the population [21]. The smartphones allow for data-based messaging, which should be considered for population scaling, as these platforms are much cheaper than SMS text messaging. Research surrounding linkage to care and the piloting, feasibility, and effectiveness of mHealth apps is needed to ensure that these interventions remain current as the population transition from basic phones to smartphones [15,19,22].

SmartLink is an mHealth app designed to provide HIV-positive smartphone owners with their laboratory results securely and rapidly, coupled with supportive information as well as prompts to link to care. Methods and information on the app development, including the challenges and limitations of the study, have been previously published [23] and will not be discussed in detail here.

Objectives

This study presents the evaluation of SmartLink to improve linkage to care for newly diagnosed HIV-positive smartphone owners through a randomized controlled trial. Of particular interest is the linkage to care of men and youth aged less than 30 years, as these populations have been historically hard to reach with traditional interventions [7-9]. Virological suppression was also evaluated as a secondary outcome.

Methods

Trial Design

The study was designed as a multisite randomized controlled trial where newly diagnosed HIV-positive participants were approached upon having a positive HIV test and were then screened for trial eligibility. Eligible and consenting trial candidates were randomized 1:1 into either the intervention or the control arm of the study. Participants in the intervention arm were then aided with the installation and setup of SmartLink.

Setting

The inner city of Johannesburg is one of South Africa's most densely populated areas, with an estimated population of 1 million people; numerous socioeconomic challenges such as

overcrowding, unemployment, crime, poverty, substance abuse, and sex work; and a high HIV prevalence [24]. The area has a well-established HIV testing and ART program, with some health care facilities providing ART to over 20,000 patients. However, the transient nature of the community makes it difficult to measure actual testing, linkage, and retention rates at the population level [25]. Participants were recruited at 5 public HIV testing sites (1 community health center, 3 clinics, and 1 tertiary hospital) from October 2015 to June 2016 and then followed up until February 2017.

Participants

Trained field workers at the 5 testing sites approached newly diagnosed HIV-positive people for trial participation after they had blood drawn for CD4 count measuring. Trial candidates were prescreened. Participants were considered for the trial if they were a resident in the area, aged 18 years and above, not pregnant, and could read English or Zulu (2 commonly understood languages in the area) [23]. Individuals were then screened for app compatibility; ineligible participants were excluded from the study if they had no active subscriber identity module card in their phone, no Android smartphone, or no data on their phone. It was discovered that the app could not be installed if the participant had insufficient RAM on their phone or if their Android version was too old (pre-version 4.2), so these parameters were also added to the exclusion criteria. Eligible participants who passed screening were then recruited into the study and randomized 1:1 into the intervention arm or the control arm using a pregenerated randomization table.

Intervention

Study staff assisted participants from the intervention arm with the installation of the SmartLink app, which was done with an Android install file and Wi-Fi dongle to allow installation at no data cost to the participants.

The app, available in English or Zulu, was designed to engage participants in their own care by directly providing them with 2 laboratory results; appointment reminders; and information about the laboratory tests, ART adherence, and HIV in general (Multimedia appendix 1). The 2 laboratory results were CD4 count and viral load, and they were communicated in simple language. These values were also expressed visually on a color-coded scale that showed *normal* values and were accompanied by a short explanation of the results and guidance as to what action, if any, should be taken.

Participants randomized into the control arm received the standard of care, where participants received counseling and were referred to their local ART initiation site to collect their laboratory results and initiate appropriate treatment as needed. All participants, regardless of the study

arm, were instructed to attend their local clinic for a follow-up within a few weeks of trial commencement and not to wait for the results on their phone.

App Security

The SmartLink logo, app icon, and landing page made no reference to HIV, AIDS, or health care to ensure that a participant's HIV or other health status would not be accidentally disclosed when viewing the app name or icon on a participant's phone. Furthermore, to protect confidential medical information from being available to other people, app security was modeled after local banking apps. This ensured security and privacy by employing a username, password, and a personal identification number to gain access to personal health data.

Outcomes

To capture HIV-related laboratory monitoring (our proxy for linkage to HIV care), evidence of an HIV-related laboratory test result between 2 weeks and 8 months of participant recruitment was sought. Test results were available on the National Health Laboratory Service (NHLS) database, which covers all local public facilities (but not initiation by private general practitioners or workplaces, although these provide very limited access in terms of absolute numbers), and included CD4, viral load, or creatinine clearance. Clinic visits were tracked after the initial 8 months until the completion of the follow-up in February 2017 to see if any lag to linkage to care was present in either trial arm. The viral load results were also analyzed to determine if virological suppression was achieved as a secondary outcome.

Due to these abovementioned independent databases as well as analytical data from the app developers, consolidation of these data was required. The investigators implemented a method to keep track of trial participants and their laboratory results by creating a centralized universal study dataset. To ensure intervention fidelity, this dataset was continuously monitored and evaluated by researchers to identify any potential variances [23].

Data Analysis

On the basis of the market research conducted in early 2015 at the study sites and a primary outcome measured as a second HIV-related laboratory test between 2 weeks and 8 months, a sample size of at least 1000 participants for each study arm was anticipated to measure a 20% difference in linkage to care between the intervention and control arms of each study subgroup such as young men. This was calculated based on a significance of .05, a power of 80%, and an estimated loss to follow-up of 27% (Hillbrow Community health Centre (CHC) data).

Descriptive statistics were used to summarize baseline characteristics, presented as categorical data with frequency (percentage). All outcomes were compared between the intervention and

control arms by linkage to care with the Pearson Chi-square test for significance. All data analyses were performed with Stata version 12.1 (StataCorp LP, College Station, TX).

The SmartLink protocol was approved by the University of Witwatersrand's Medical Human Research Ethics Committee (Certificate: M150606), the City of Johannesburg, and Gauteng's Department of Health at the provincial level and was registered in ClinicalTrials.gov (NCT02756949).

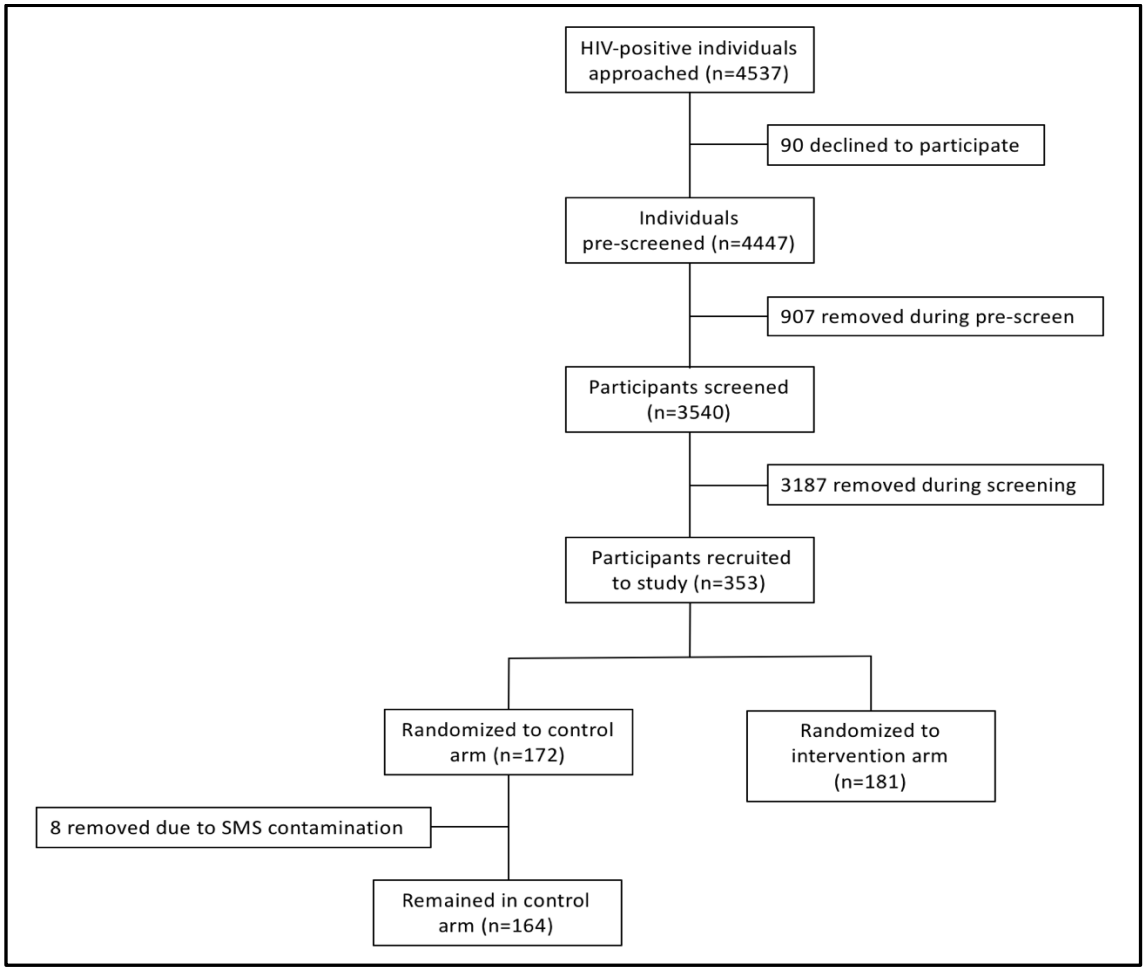

Figure 1. SmartLink participant flow diagram.

Abbreviations: HIV, human immunodeficiency virus; n, number; SMS, short message service

Results

Participant Flow

The participant flow diagram is shown in Figure 1. Of the 4537 individuals approached about the study, only 90 people (2.0%) declined to participate; however, a total of 4094 people (90.2%) were found to be ineligible during the prescreening and screening. The data from 8 participants in the control arm were also removed from analysis because of the erroneous sending of SMS reminders for their 6-month clinic appointment. Once removed, 164 participants (3.6%) remained in the control arm, and 181 participants (4.0%) remained in the intervention arm. A complete breakdown of enrollment based on inclusion and exclusion criteria has been reported [23].

Table 1. Baseline characteristics of SmartLink trial participants.

Characteristic		Control n=164 (%)[a]	Intervention n=181 (%)	Total n=345 (%)
Sex				
	Male	61 (37.2%)	60 (33.1%)	121 (35.1%)
	Female	103(62.8%)	121 (66.9%)	224 (65.9%)
Age				
	18-30	69 (42.1%)	83 (45.9%)	152 (44.1%)
	31+	95 (57.9%)	98 (54.1%)	193 (55.9%)
Country of Birth				
	South Africa	95 (57.9%)	103 (56.9%)	198 (57.4%)
	Zimbabwe	61 (37.2%)	63 (34.1%)	124 (35.9%)
	Other	8 (5.9%)	15 (8.3%)	23 (6.67%)
Education				
	Primary only	6 (3.7%)	8 (4.4%)	14 (4.1%)
	Some secondary school	44 (26.9%)	51 (28.2%)	95 (27.5%)
	Completed secondary school	85 (51.8%)	98 (54.1%)	183 (53.0%)
	Attended/completed tertiary	29 (17.7%)	24 (13.3%)	53 (15.4%)
Employment Status				
	Employed full time	79 (48.2%)	82 (45.3%)	161 (46.7%)
	Employed part time	22 (13.4%)	37 (20.4%)	59 (17.1%)
	Unemployed	40 (24.4%)	49 (27.1%)	89 (25.8%)
	Self employed	16 (9.8%)	10 (5.5%)	26 (7.5%)
	Student	7 (4.4%)	3 (1.7%)	10 (2.9%)

[a]Totals may not add to 100% because of decimal rounding.

Baseline Characteristics

There were no significant differences in the baseline characteristics between the intervention and control arms (Table 1). Overall, only one-third of the participants were male (35.1%) and nearly half (44.1%) were youth aged less than 30 years. Almost half of the participants were employed full time (46.7%) and the majority had at least attended secondary school (95.9%). In

addition, 57.4% of the participants were South African and just over one-third (35.9%) were from Zimbabwe. These baseline characteristics reflect the demographics of inner-city Johannesburg, where many migrants from Zimbabwe have settled and become part of the local population. These migrants are often well educated and possibly more likely to be employed than South Africans living in the inner city.

Primary Outcome: Linkage to Care

This study called for a sample size of 2000 total participants; however, because of several challenges and limitations outlined, recruitment numbers were much lower than anticipated at 345 [23].

Table 2. Linkage to care.

Group		Linked to care 2 weeks to 8 months			Ever linked to care		
		NLC n (%)	LC n (%)	Total	NLC n (%)	LC n (%)	Total
Total Cohort							
	Control	90 (54.9%)	74 (45.1%)	164	64 (39.0%)	100 (61.0%)	164
	Intervention	93 (51.4%)	88 (48.6%)	181	65 (35.9%)	116 (64.1%)	181
	Total	183 (53.0%)	162 (47.0%)	345	129 (37.4%)	216 (62.6%)	345
		Pearson $chi^2(1)$ = 0.4224 p = 0.516			Pearson $chi^2(1)$ = 0.3561 p= 0.551		
Males							
	Control	32 (52.5%)	29 (47.5%)	61	20 (32.8%)	41 (67.2%)	61
	Intervention	27 (45.0%)	33 (55.0%)	60	20 (33.3%)	40 (66.7%)	60
	Total	59 (48.4%)	63 (51.6%)	121	40 (33.1%)	81 (66.9%)	121
		Pearson $chi^2(1)$ = 0.6736 p = 0.412			Pearson $chi^2(1)$ = 0.0041 p= 0.949		
Females							
	Control	58 (56.3%)	45 (43.7%)	103	44 (42.7%)	59 (57.3%)	103
	Intervention	66 (54.6%)	55 (45.5%)	121	45 (37.2%)	76 (62.8%)	121
	Total	124 (55.4%)	100 (44.6%)	224	89 (39.7%)	135 (60.3%)	224
		Pearson $chi^2(1)$ = 0.0702 p= 0.791			Pearson $chi^2(1)$ = 0.7101 p = 0.399		
Youth 18-30							
	Control	47 (68.1%)	22 (31.9%)	69	34 (49.3%)	35 (50.7%)	69
	Intervention	39 (47.0%)	44 (53.0%)	83	25 (30.1%)	58 (69.9%)	83
	Total	86 (56.6%)	66 (43.4%)	152	59 (38.8%)	93 (61.2%)	152
		Pearson $chi^2(1)$ = 6.8461 **p = 0.009**			Pearson $chi^2(1)$ = 5.8210 **p = 0.016**		
Over 30							
	Control	43 (45.3%)	52 (54.7%)	95	30 (31.6%)	65 (68.4%)	95
	Intervention	54 (55.1%)	44 (44.9%)	98	40 (40.8%)	58 (59.2%)	98
	Total	97 (50.3%)	96 (49.7%)	193	70 (36.3%)	123 (63.7%)	193
		Pearson $chi^2(1)$ = 1.8679 p= 0.172			Pearson $chi^2(1)$ = 1.7807 p = 0.182		

[a]NLC: not linked to care. [b]LC: linked to care.

Total Cohort

Linkage to HIV care between 2 weeks and 8 months was just under 50% (45.1% control vs 48.6% intervention; *P*=.516) and increased to just over 60% (61.0% control vs 64.1% intervention; *P*=.551) after the initial 8-month period (Table 2).

Males

The male population, which was of specific interest, showed a slightly higher (but not statistically significant) linkage to care with the app between 2 weeks and 8 months (47.5% control vs 55.0% intervention; *P*=.412), but after 8 months, both these values were similar, approximately 66% (67.2% control vs 66.7% intervention; *P*=.949).

Youth Aged Between 18 and 30 Years

Despite the small sample size, a statistically significant difference was seen with youth aged between 18 and 30 years. Linkage to care between 2 weeks and 8 months was approximately 20% higher for youth with the app (31.9% control vs 53.0% intervention; *P*=.009), and this remained true after 8 months as well (50.7% control vs 69.9% intervention; *P*=.016; Table 2).

Secondary Outcome: Viral Load Suppression

For participants who had viral load tests in the NHLS database, virological suppression was assessed as an outcome. As recruitment numbers were much lower than anticipated, participant results were also low, and no statistically significant results were reached; however, these values are presented for completeness (Table 3). As of February 2017, a total of 83 participants had viral load tests that could be used for analysis, 39 out of 164 (23.8%) from the control arm and 44 out of 181 (24.3%) from the intervention arm. With viral load suppression defined as less than 400 copies/mL, 59.0% of the control arm and 63.6% of the intervention arm experienced suppression; however, the *P* value of .663 negated any significance.

Table 3. Viral load suppression.

Study group	Virally suppressed				
	Yes, n (%)	No, n (%)	Total, n (%)	Pearson χ^2	P value
Intervention	28 (63.6)	16 (36.4)	44 (100.0)		
Control	23 (59.0)	16 (41.0)	39 (100.0)		
Total	51 (61.5)	32 (38.6)	83 (100.0)		
				0.2	.66

Discussion

Principal Findings

Although this was the first evaluation using a smartphone-enabled app to support linkage to HIV care in Africa, as far as we are aware, the study outcomes were limited due to being underpowered as a result of complications and limitations surrounding app compatibility. As a proof of concept, the SmartLink app worked as anticipated; however, the smartphone specifications required for installation excluded over 90% of candidates who volunteered to participate in the study. This is unfortunately a common trend in mHealth studies, where many interventions show generally positive results; however, they are often inconclusive or are not substantial enough when extrapolated out to a broader population or scaled up [16,26].

Although this study demonstrated that app-linked information and prompting can lead to increased linkage to care, the specific technology was not evaluated. The SmartLink app provided patients with laboratory results, information, and appointment reminders, but the relative efficacy of these specific components could not be explored. Despite the challenges in trial enrolment, one population of interest, youth aged 18 to 30 years, showed a statistically significant benefit of the app. This subpopulation experienced a 20% increase in linkage to care for the app group, and this is encouraging as HIV patients in this age group have historically been very difficult to engage with traditional interventions [8]. In South Africa, this population is 16% more likely to own a smartphone and 19% more likely to access the internet with their phone than their parents [27]. The high smartphone ownership coupled with our evidence of increased linkage in care strongly suggests that mHealth apps for engagement in care should be considered for this age group.

This demographic will become more and more familiar with technology, reinforcing the need to create a strong body of evidence surrounding these mHealth interventions. For children aged 9 to 17 years, 80% have access to internet on a smartphone and 84% own their own device. This generation is growing up with the internet, social media, and apps and already possesses the same mobile skills set as their parents, with children even surpassing them with knowledge about creating media and installing apps [28]. Future studies should focus on tailoring mHealth interventions toward youth, while also providing an opportunity to standardize counseling and support communications from health care providers [29].

Conclusions

This proof-of-concept study has demonstrated that SmartLink can significantly increase linkage to care for youth aged 18 to 30 years; however, further evaluation with larger samples is required to recommend such an intervention for programmatic rollout. This research is of timely importance as demand for entry-level smartphones (sub-US $100) in developing countries had

led to over 400 million smartphone units being sold in the first quarter of 2018 alone [30]. As smartphone penetration increases and prices decrease, new innovations such as using quick response code technology coupled with patient-held smartcards can allow for information to be transferred without internet access or data [31]. During this shift, mHealth apps should also be considered for incorporation into multifaceted interventions as bundling apps with SMS text messaging, phone calls, or in-person communications could be a way to optimally engage patients while app familiarity and technology continue to improve [32].

Limitations

Secondary outcomes, such as ART initiation rates, feasibility, satisfaction, and participants' knowledge, could not be evaluated because of the limitations, as outlined by Venter et al in 2018 [23]. Analytics on app use by participants also could not be evaluated because of complications in data collection between the devices and the back-end analytics software. Essentially, data exchange between the relevant systems could not be achieved during the trial, limiting the scope of log-in analytics to counts of app openings only. Finally, we acknowledge the limitations of the trial in terms of generalizability, as already mentioned. The eligibility criteria lead to a selected patient group. For instance, a relatively high proportion of Zimbabwean patients and more educated patients were better able to qualify for the trial.

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Conflicts of Interest

None declared.

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CHAPTER 5. Changes in Perceptions and Use of Mobile Technology and Health Communication in South Africa During the COVID-19 Lockdown: Cross-sectional Survey Study

This chapter is based on:

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Abstract

Background

In late March 2020, South Africa implemented a 5-stage COVID-19 Risk Adjusted Strategy, which included a lockdown that required all residents to remain home to prevent the spread of COVID-19. Due to this lockdown, individuals have been forced to find and use alternatives for accomplishing tasks including shopping, socializing, working, and finding information, and many have turned to the internet and their mobile devices.

Objective

This study aimed to describe how South Africans consume and internalize information surrounding the COVID-19 outbreak in order to determine whether the COVID-19 lockdown and social isolation have influenced technology behavior, particularly in terms of health communication and information.

Methods

From June 24 to August 24, 2020, people in South Africa were invited to complete a survey through the Upinion mobile app, an online data collection resource. The survey collected information on demographics, and technology use during the lockdown, and COVID-19 knowledge.

Results

There were 405 participants, of which 296 (73.06%) were female. A total of 320 (79.01%) participants had a tertiary school education, 242 (59.75%) were single, and 173 (42.72%) had full-time employment. The lockdown forced 363 (89.63%) participants to use more technology, especially for work (n=140, 24.05%) and social media/communication (n=133, 22.85%). Security or privacy issues (n=46, 38.98%) and unfamiliarity with technology (n=32, 27.12%) were identified as the most common issues faced by the 127 (31.36%) participants who were unsure about using technology prior to the lockdown. Almost all participants (n=392, 96.79%) stated that they would continue using technology after the lockdown. Multimedia (n=215, 53.09%), mobile phone content (n=99, 24.44%), and health organizations and professionals (n=91, 22.47%) were the main sources of COVID-19 information. Most participants (n=282, 69.63%) felt that they had enough information. Two-thirds (n=275, 67.90%) of participants stated that they had used their mobile phones for health information before the lockdown, with web searches (n=109, 26.91%), social media (n=58, 14.32%), and government and institutional websites (n=52; 12.84%) serving as their main sources of information. Overall, the mean COVID-19 knowledge score was 8.8 (out of 10), and 335 (82.72%) had adequate knowledge (scored ≥8). Males were less likely to identify the correct transmission routes, and single participants were less likely to identify the signs and symptoms of the coronavirus. Tertiary school graduates were 4 times more likely to correctly identify the routes and 2 times more likely to identify how to stop the spread of the virus. People aged 43-56 years were 4 times more likely to identify how the coronavirus can be prevented, and participants ≥57 years were 2.6 times more likely to obtain a knowledge score of 10 when compared to those under 29 years of age.

Conclusions

This study has shown that the COVID-19 lockdown has forced people to increase technology use, and people plan to continue using technology after the lockdown is lifted. Increased technology use was seen across a variety of fields; however, barriers including privacy, unfamiliarity, and data costs were identified. This population showed high COVID-19 knowledge, although the use of web searches and social media, instead of government and institutional websites, increases the potential for health misinformation to be spread.

Introduction

On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic [1]; thereafter, many countries followed China's "lockdown" approach to reduce new cases. In March 2020, South Africa began a 21-day, level 5 lockdown as part of a 5-stage COVID-19 Risk Adjusted Strategy. During this period, only hospitals, clinics, grocery stores, and pharmacies remained open, and only essential personnel (eg, doctors, nurses, police) were permitted to leave their homes, although there were some controlled exceptions for medical care or essential supplies like food and medicine [2].

During the lockdown, cases and preventative measures have been well documented and investigated, both globally and in South Africa [3,4]. However, the behavioral effects of the lockdown are not as well known. With social distancing, individuals have been forced to find and use alternatives to accomplish tasks such as shopping, working, attending school, and staying informed, and many have turned to their mobile devices. In China there was a 30% increase in app use during their lockdown [5-7], while a global analysis of five popular social media platforms (Twitter, Instagram, YouTube, Reddit, and Gab) identified 8 million COVID-19–related posts and comments over the first 45 days of 2020 [8].

In a sense, this is all forced use of technology since people have limited alternatives to meet their needs, and to engage with this captive audience, many governments and institutions have introduced mobile health (mHealth) interventions to disseminate information during the pandemic [9-12]. Specifically, the South African government has implemented a website that provides information on COVID-19, the Risk Adjusted Strategy, preventative measures, news and updates, and links to other resources [13]. These additional resources include a WhatsApp support line, an emergency telehealth hotline, social media message campaigns, and updates from the South African Government and National Department of Health websites [3,13,14].

With all of this electronic communication resulting from COVID-19, researchers have taken the opportunity to investigate how it has influenced digital health, and a variety of studies have already been conducted. Some studies have harnessed big data to predict outbreak hotspots with algorithm-based web mining [8,15-17], while others have looked at how individuals share and consume COVID-19–related content [18]. A study from India showed that more than half of participants (n=58, 56.3%) had adequate information regarding COVID-19; however, their primary source of information was from multimedia (radio, TV, newspaper) (n=57, 55.3%), and only 22 (21.4%) relied on the internet as their main source for information [19].

Despite high mobile penetration in low- and middle-income countries [20,21], there are still individuals who have not embraced technology for various reasons, including security and privacy concerns, data costs, and an inability to understand modern electronics [22]. With the limitations set by the lockdown, increased exposure to technology may have altered some people's perceptions and use of technology. This study aimed to describe how South Africans consume and internalize information surrounding the COVID-19 outbreak to assess whether the COVID-19 lockdown and social isolation has influenced technology behavior, particularly for health communication and information.

Methods

Study Design

This South African cross-sectional study was conducted electronically, administered through the Upinion mobile app, an online data collection resource. Participants were included if they were an existing or new Upinion user with current access to surveys on the app, ≥18 years of age, and able to provide online consent. Individuals were excluded if they were not able to access the Upinion app, were younger than 18 years, or refused to participate.

Data Collection

From June 24 to August 24, 2020, existing and new Upinion users were invited to complete a survey through Upinion notifications and advertisements on social media platforms, respectively. Once an individual agreed to participate in the current study, they were able to provide informed consent through the app and then register for the survey group [23]. The participant was then given access to the survey, which was completed through their mobile phone. During the survey, all answers were recorded electronically in the backend of the app.

A mobile app was used to collect data as this was deemed the easiest way to gather responses, while obeying the lockdown restrictions and ensuring the safety of both participants and data collectors. This method of online distribution of a survey and accompanying electronic consent has been used with increasing frequency, particularly during the COVID-19 pandemic for studies with similar methodologies [19,24-27].

The Upinion App

The Upinion messaging and data collection app was developed in 2014 by Upinion, a people-centric research technology company based in the Netherlands, and its use in Southern African Development Community countries is licensed to Opinion Solutions. The app was developed as a way to collect feedback from affected communities in any response effort in order to provide better and more efficient support. It serves as an outlet for those affected by crisis to share their unique problems, needs and solutions, so that nongovernmental organizations have a grass-roots understanding of the situation on the ground, allowing for tailored interventions. This has been used by nonprofit organizations like Oxfam to identify the needs of refugee communities [23], and research institutes like the Wits Reproductive Health and HIV Institute to administer health-related surveys directly via participants' mobile phones [28]. Upinion does not collect personal data, but rather personal data is collected through survey questions and the participant shares this voluntarily. Upinion encrypts all mobile phone numbers and IP addresses in compliance with General Data Protection Regulation and is also ISO/IEC (International Organization for Standardization/International Electrotechnical Commission) 27001 certified. Screenshots of the Upinion app are presented in Figure 1.

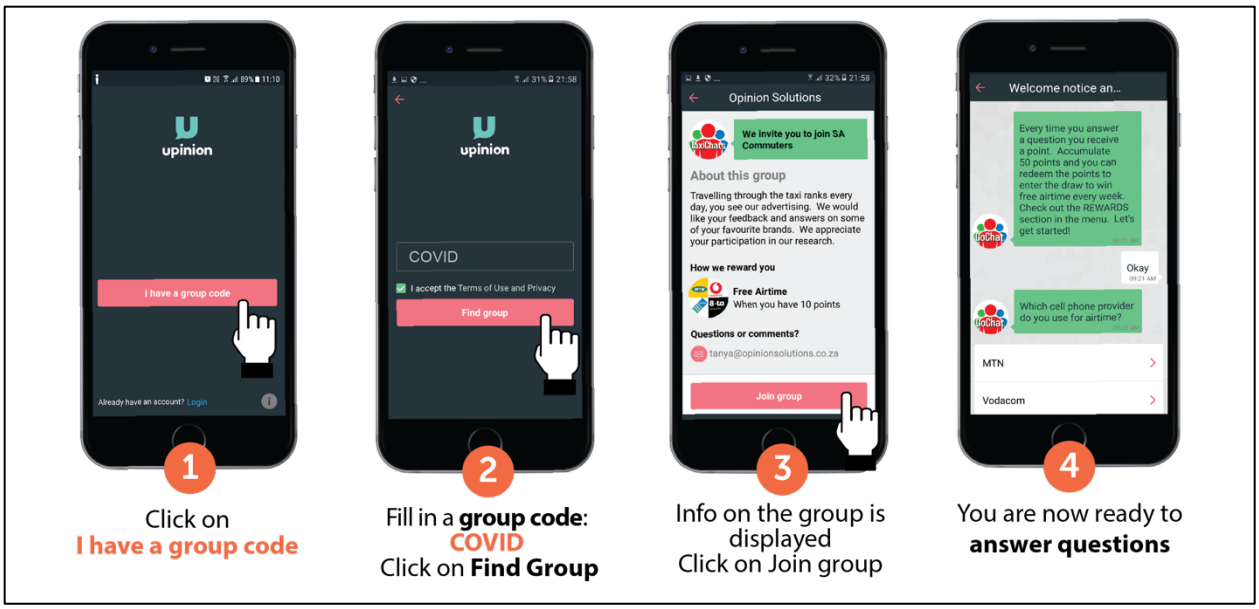

Figure 1. The Upinion app.

Survey Development

This survey was adapted from the survey Demographic Data and Structure Knowledge Questionnaire Regarding Prevention of COVID-19, used in a similar study from India [19]. The original questionnaire consists of two sections—the first comprising 8 questions to explore demographic information and the second 10 questions that focused on COVID-19 knowledge. In our survey (Multimedia Appendix 1)[10], we have modified the sections on demographic information and COVID-19 knowledge to reflect the South African context, and a third section was added to explore participants' technology use during the COVID-19 outbreak.

Data Analysis

Upinion has a built-in dashboard to monitor responses in real time; however, the final data set was exported to Excel (Microsoft Corp) for cleaning and coding, then exported to Stata V.15 (StataCorp) for analysis. Demographic information, technology use, and COVID-19 knowledge questions were all described as frequency and percentages. A mean knowledge score (with standard deviation) was also calculated across all 10 knowledge questions, with a score below 6 considered inadequate knowledge, 6-8 considered moderately adequate knowledge, and a score above 8 considered adequate knowledge [19].

The Pearson chi-square test was used to assess trends of association between outcome variables (COVID-19 knowledge and technology use) and demographic characteristics. Logistic regression models (bivariate [not included in this paper] and multivariable models) were constructed for the

[10] https://jmir.org/api/download?alt_name=formative_v5i5e25273_app1.docx&filename=9d9f7d98dbb8d59c493511f56187a55b.docx

outcome variables to control for confounders and identify independent predictors. These predictors were reported as crude (not included in this paper) and adjusted odds ratios (aOR), with 95% CI and P values (<.05 was considered significant).

Ethical Consideration and Approval

Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (nonmedical) (reference number 200512). Survey respondents did not receive any compensation for participation.

Results

Demographics

Participants' demographic data are presented in Table 1. Of the 405 participants, 84 (20.74%) were 28 years or younger, 165 (40.74%) were between the ages of 29 and 42 years, 110 (27.16%) were between the ages of 43 and 56 years, and 46 (11.36%) were 57 years or older. There were 296 (73.06%) females, 320 (79.01%) participants had completed tertiary school education, and 242 (59.75%) were single. A total of 173 (42.72%) participants had full-time employment, 74 (18.27%) were casually employed, 29 (7.16%) were students, and 129 (32.85%) were unemployed.

Table 1. Demographic characteristics.

Demographic (n=420)	Frequency	Percentage (%)*
Age		
18-28 years old	84	20.74
29-42 years old	165	40.74
43-56 years old	110	27.16
57 years or older	46	11.36
Sex		
Female	296	73.09
Male	109	26.91
Education		
Primary school or less	1	0.25
Secondary school	84	20.74
Tertiary school (any)	320	79.01
Marital status		
Married	163	40.25
Single	242	59.75
Employment status		
Casually employed	74	18.27

Full-time employment	173	42.72
Student	29	7.16
Unemployed	129	31.85

*Percentages may not add up to 100.0% due to rounding.

Technology Use

A total of 363 (89.63%) participants stated that the lockdown had forced them to use more technology, and the greatest increases in use were for work (n=140, 24.05%), social media/communication (n=133, 22.85%), shopping (n=78, 13.4%), and news and information (n=70, 12.03%). Nearly one-third (n=127, 31.36%) of participants stated that they were unsure about using technology before the lockdown, with security and privacy issues (n=46, 38.98%) and unfamiliarity with technology (n=32, 27.12%) identified as the most common concerns. More than half (n=209, 51.60%) the participants had positive feelings about the increased forced technology use, while almost all (n=392, 96.79%) participants stated that they would continue using technology after the lockdown. When asked about information regarding COVID-19, 282 (69.63%) felt that they had enough information and knowledge, with multimedia (n=215, 53.09%), mobile phone content (n=99, 24.44%), and health organizations and professionals (n=91, 22.47%) as their main source of COVID-19 information. Two-thirds (n=275, 67.90%) of participants stated that they had used their mobile phones for health information before the COVID-19 outbreak, with web searches (n=109, 26.91%), social media posts (n=58,14.32%), government and institutional websites (n=52, 12.84%), and mobile apps (n=58, 14.32%) serving as their main sources of health information (Table 2).

Table 2. Technology use

Technology questions (n=420)	Frequency	Percentage (%)*
Has the lock down forced you to use more technology?		
Yes	363	89.63
No	42	10.37
If yes, what do you use technology for?		
Job searching	33	5.67
Social media/communication	133	22.85
Education	58	9.97
Shopping	78	13.40
Entertainment	48	8.25
Work	140	24.05
News and information	70	12.03
Banking	16	2.75
Religion	6	1.03
Where you unsure about using technology/ online methods before?		

Yes	127	31.36
No	278	68.64
If yes, what made you feel uncomfortable?		
Security/privacy issues	46	38.98
Unfamiliar with technology	32	27.12
Lack of personal connection/accountability	16	13.56
Cost of data and devices	10	8.47
Reliability issues	14	11.86
How do you feel about the increased forced use of technology?		
Positive feelings	209	51.60
Neutral/mixed feelings	129	31.85
Negative feelings	67	16.54
Will you continue to use technology after the lock down?		
Yes	392	96.79
No	13	3.21
Do you have enough information/knowledge regarding SARS-CoV-2?		
Yes	282	69.63
No	123	30.37
What is your main source of information for SARS-CoV-2?		
Health organizations and professionals	91	22.47
Mobile phone content	99	24.44
Multimedia (Radio, television, newspaper)	215	53.09
Have you used your mobile phone for health information before the SARS-CoV-2 outbreak?		
Yes	275	67.90
No	130	32.10
If yes, what was your main source of health information?		
Email	1	0.25
Government/institutional websites	52	12.84
Messaging platforms (WhatsApp, SMS)	17	4.20
Mobile apps	38	9.38
Social media posts	58	14.32
Web searches (ex. Google)	109	26.91

*Percentages may not add up to 100.0% due to rounding.

Logistic regression analysis identified relationships between demographics and four technology use variables (Multimedia Appendix 2)[11]. When asked if the lockdown had forced participants to use more technology, participants with a tertiary school education were 2.5 times more likely to

[11] https://jmir.org/api/download?alt_name=formative_v5i5e25273_app2.docx&filename=80f956bf8e61ff4d5b1029a243c77020.docx

increase their technology use than those with a primary or secondary school education (AOR=2.580;CI=1.212-5.489,P=0.014) and full-time employees were also less likely to increase their technology use compared to those casually employed (AOR=0.275; CI=0.078-0.966,P=0.044).

Regarding the main source of SARS-CoV-2 information, multimedia, health organizations and professionals and mobile phone content all had demographic associations. Tertiary school graduates were less likely to use multimedia as their main source of SARS-CoV-2 information compared to those with primary or secondary school education (AOR=0.536;CI=0.319-0.900,P=0.018). Multimedia was almost two times more likely to be the main source of information in respondents 29-42 years old, when compared to those younger than 29 years old(AOR=1.862;CI=1.062-3.378,P=0.041). Single participants were less likely to use health organizations and professionals (AOR=0.537;CI=0.318-0.906,P=0.020) as their main source of SARS-COV-2 information. Mobile phone content was also associated with age, with the 57–70 year old group being least likely (AOR=0.339;CI=0.128-0.896,P=0.029) to use their mobile as the main source of health information compared to those younger than 29 years old.

Considering having enough information/knowledge about SARS-CoV-2 age, being male, being single and having a tertiary education were all associated. The 57–70 year old group were approximately 6 times (AOR=5.661;CI=1.894-16.925,P=0.002) more like to have adequate knowledge compared to those younger than 29 years old. Males were almost twice as likely (AOR=1.892;CI=1.094-3.272,P=0.022) than females to have enough SARS COV-2 knowledge as were those having a tertiary school education (AOR=1.885;CI=1.111-3.198,P=0.019) over those with a secondary education or lower, while single participants were less likely (AOR=0.509;CI=0.297-0.873,P=0.014) to have adequate knowledge.

The oldest age group were the least likely (AOR= 0.184;CI=0.075-0.449,P<0.001;) to use their phone for health information prior to the pandemic as were students (AOR=0.277;CI=0.311-0.127,P=0.010).

COVID-19 Knowledge

When asked about COVID-19, 358 (88.40%) participants correctly identified it as a contagious respiratory virus, and 392 (96.79%) correctly stated that it was transmitted through respiratory droplets. Over three-quarters (n=319, 78.77%) of participants correctly chose all the ways that the virus could be spread; the rest thought it was only spread by coughing or sneezing (n=52, 18.84%), by touching objects that have COVID-19 droplets on them (n=17, 4.2%), or through close contact with an infected individual (n=16, 3.95%). All of the common COVID-19 symptoms (cough, sore throat, fever, and shortness of breath) were correctly identified by 379 (93.58%)

participants; the same percentage correctly identified all encouraged prevention techniques (avoid touching one's face, avoid contact with sick people, and wash hands thoroughly). When asked about handwashing duration, 20 seconds was correctly selected by the majority (n=340, 83.95%). For the question on how to stop the spread of COVID-19, 368 (90.86%) correctly chose social distancing, self-isolation, and regular handwashing as their response, and when asked how to stop the chance of spreading the virus, 383 (94.57%) correctly chose coughing and sneezing into their elbow, social distancing and self-isolation, and regular handwashing as their response. Most participants (n=308, 76.05%) correctly stated that they would call the emergency hotline or WhatsApp support line if they thought they had COVID-19 symptoms, although 79 (19.51%) incorrectly stated that they would rush to the nearest hospital for testing. Lastly, practicing social distancing, self-isolation, and washing one's hands thoroughly were all correctly identified by 369 (91.11%) participants as the key to prevent the spread of COVID-19 (Table 3).

Table 3. Structured COVID-19 questionnaire

SARS-CoV-2 questions (n=420)	Frequency	Percentage (%)*
What is Novel Coronavirus (COVID-19)?		
It is a bioweapon	11	2.72
It is a sexually transmitted infection	4	0.99
It is a very contagious respiratory virus	358	88.40
It is just another term for the common cold	22	5.43
It is transmitted through respiratory droplets	10	2.47
What are transmission routes of COVID-19?		
It is transmitted by eating Chinese food	4	0.99
It is transmitted through direct blood contact	6	1.48
It is transmitted through respiratory droplets	392	96.79
It is transmitted through sexual intercourse	3	0.74
How the coronavirus can be spread?		
By touching objects that have COVID respiratory droplets	17	4.20
Through close contact with an infected individual	16	3.95
Through coughing or sneezing	52	12.84
All of the above	319	78.77
(blank)	1	0.25
What are the signs and symptoms of coronavirus?		
Cough and sore throat	11	2.72
Fever	15	3.70
Shortness of breath	12	2.96
All of the above	367	90.62
Corona virus can be prevented by		
Avoid touching your face	8	1.98

Avoiding contact with sick people	7	1.73
Wash your hands thoroughly	11	2.72
All of the above	379	93.58
Wash your hands with soap or sanitizer for at least		
5 seconds	5	1.23
10 seconds	17	4.20
20 seconds	340	83.95
1 minute	43	10.62
To stop spread corona virus you should		
Practice social distancing	17	4.20
Practice social distancing, Wash your hands thoroughly	1	0.25
Self-isolate	16	3.95
Self-isolate, Practice social distancing	1	0.25
Wash your hands thoroughly	2	0.49
All of the above	368	90.86
How can you stop the chance of spreading corona virus?		
Cough or sneeze into a tissue or your elbow	4	0.99
Self-isolate and practice social distancing	13	3.21
Wash your hands thoroughly	5	1.23
All of the above	383	94.57
What will you do when suspected that you have symptoms of coronavirus?		
Call emergency hotline or WhatsApp support line	308	76.05
Go to the pharmacy to get medication	9	2.22
Rush to nearest hospital for testing	79	19.51
Stay in close physical contact with friends/family for support	8	1.98
(blank)	1	0.25
Important key to prevent from spreading of COVID-19 is?		
Practice social distancing	10	2.47
Self-isolate	18	4.44
Wash your hands thoroughly	7	1.73
All of the above	369	91.11
Total knowledge score		
Inadequate (scores 5 and below)	19	4.69
Moderately adequate (scores 6 and 7)	51	12.59
Adequate (scores 8 and above)	335	82.72

*Percentages may not add up to 100.0% due to rounding.

Overall, the mean knowledge score was 8.8 (SD 1.53). There were only 19 (4.69%) participants with inadequate knowledge, 51 (12.59%) with moderately adequate knowledge, and 335 (82.72%) with adequate knowledge (Table 3).

Logistic regression analysis identified relationships between demographics and 4 COVID-19 knowledge variables. Males were less likely to identify the correct transmission routes of COVID-19 (aOR 0.216; 95% CI 0.063-0.744, P=.02) than females, while those with a tertiary education were 4 times more likely to correctly identify the routes (aOR 4.414; 95% CI 1.308-14.900, P=.02) than those with only primary or secondary education. Tertiary school graduates were also 2 times more likely to identify how to stop the spread of the virus (aOR 2.215; 95% CI 1.041-4.714, P=.04), compared to participants with only primary or secondary education. Single participants were less likely to identify the signs and symptoms of COVID-19 (aOR 0.182; 95% CI 0.052-0.631, P=.01) than married participants. The 43-56 years age category was 4 times more likely to identify how COVID-19 can be prevented (aOR 3.987; 95% CI 1.011-15.718, P=.048) compared to those under 29 years of age (Multimedia Appendix 3)[12].

Lastly, association analyses conducted separately between demographics and the outcome variables (COVID-19 knowledge scores and technology use) only identified a significant relationship in participants ≥57 years being 2.6 times more likely to obtain a knowledge score of 10 (aOR 2.60; 95% CI 1.1-6.0, P=.03) when compared to participants 28 years and under.

Discussion

Principal Findings

This study is the first to describe how South Africans interact with technology and consume health information during the current COVID-19 outbreak. Our findings were in line with a similar study from India [19]. Multimedia was the main source of COVID-19 information for both countries (India: n=57, 55.4% vs South Africa: n=215, 53.09%), followed by the internet in India (n=22, 21.4%) and mobile phone content in South Africa (n=99, 24.44%). Despite more people in India stating that they had adequate COVID-19 information (India: n=98, 95.1% vs South Africa: n=282, 69.63%), the South African mean knowledge score of 8.8 was slightly higher than that of India (8.01). The South African study also showed that the lockdown has forced the majority of participants to increase their technology use and these findings are in line with similar increases in technology use from around the world [5-7,29-31]. Participants with a tertiary school education were more likely to increase their technology use than those with less education, who were less likely to use multimedia as their main source of COVID-19 information. This is in line with a study from sub-Saharan Africa, which showed that the positive effects of mobile phone

[12] https://jmir.org/api/download?alt_name=formative_v5i5e25273_app3.docx&filename=dcd5a246868301959b9cb8b1b39bb826.docx

use is diminished by poor primary education [32]. However, in addition, these findings may be explained by socioeconomic factors associated with more education, as college graduates earn higher wages and are better equipped to cope with economic shocks [33]. Full-time employees were less likely to increase their technology use compared to those who were causally employed, although this may be due to a higher baseline of technology use for full-time employees due to the growing demands of the knowledge economy [34].
The rise in South African technology use has also been validated by the nation's data usage, which increased by more than one-third over the first few days of the lockdown [35]. This increase in technology use led the government to quickly digitize education through a combination of free electronic readers and zero-rated educational apps and websites. This has allowed schools to move to an online curriculum, which has facilitated the return to studies via home-based schooling for many students, by mid-March 2020 [29]. Similarly, apps and websites are also being used by the National Department of Health to relay COVID-19 information to the public [3,13,14]; however, there are many other online sources for COVID-19 information.

Government or institutional websites [3,4,13,14] publish evidence-based information and fact check their findings; however, more participants stated that their main mobile source of health information was web searches or social media posts. Unfortunately, web searches and social media posts are not regulated, and the sharing of misinformation has created an infodemic surrounding COVID-19 [8,25]. This misinformation includes false news articles, conspiracy theories surrounding the virus creation, ineffective home remedies for treatment, and downplaying of the need for prevention control, such as social distancing and mask use. The propagation of this misinformation can actually present a health risk and may undermine the countermeasures implemented by governments and credible institutions [8,36]. Despite a high overall knowledge score, misinformation may have played a role in this study, as two questions (How COVID-19 can be spread? and What will you do if you suspect that you have symptoms of COVID-19?) scored below adequate. These questions may identify knowledge gaps where increased outreach is needed to educate the population, especially for the second question, where 79 (19.51%) participants stated that they would rush to the nearest hospital for testing instead of calling the emergency hotline or WhatsApp support line for further instructions. There are a number of documented ways to engage users on mobile platforms, and the government can use them to dispel misinformation by guiding people to accurate information sources. Social media outreach, with dialogue loops, is a particularly effective way to engage with individuals, and this type of social media outreach can be tailored with specific messages that target specific subpopulations [37,38].

Misinformation may have disproportionately affected participants under the age of 29 years, especially when compared to those above 57 years. The older group was less likely to use their

mobile as the main source of health information, yet they were 6 times more likely to have enough COVID-19 information, and 2.6 times more likely to obtain a knowledge score of 10. In South Africa, youth under 30 years are almost 20% more likely to use their phone to access the internet than their parents, which would expose the younger age group to more online misinformation than the oldest age group [39]. Single participants were less likely to use health organizations and professionals as their source of COVID-19 information, and not using a trusted source may have also led to misinformation, as they were less likely to have enough COVID-19 information and correctly identify COVID-19 signs and symptoms. Having enough COVID-19 information may not be a true indicator of knowledge though since males were twice as likely to say they had enough COVID-19 information but were less likely to identify the correct routes of COVID-19 transmission.

This study has also reiterated some known barriers to mobile use in South Africa, such as security and privacy issues, unfamiliarity with technology, and data costs. Due to an increase in data usage, some local networks have temporarily lowered data costs [35], but long-term affordable data plans are required to ensure equitable mobile usage for the duration of this lockdown and in the future [40]. Security and privacy issues have been well documented in South Africa, especially for mHealth platforms [22,41,42]. However, previous studies have shown that personal identification number (PIN)–protected mobile platforms for delivering sensitive health information are feasible and acceptable in South Africa [42,43]. Furthermore, a Japanese study that investigated online consumption suggests that the process of making online purchases for the first time during the lockdown has facilitated people becoming familiar with technology, thus alleviating some perceived barriers [44]. This information provides context to the 392 (96.8%) participants who stated they will continue to use technology after the pandemic. However, follow-up studies must be conducted to quantify this.

Limitations

A selection bias may be present due to the device and data requirements needed to access this survey, which was conducted online via a convenience sample. As this survey was adapted from a pre-existing survey, it was not validated or pilot tested in South Africa before this study. Furthermore, participants were asked to self-report their technology use, and no measurements were taken to validate these statements.

Conclusion

This study has shown that the COVID-19 lockdown has forced many people to increase technology use, and almost all participants will continue to use technology post lockdown. Increased technology use was seen across a variety of fields; however, well-known barriers were cited, including privacy and security concerns, unfamiliarity with technology, and data costs. This

population showed high COVID-19 knowledge, but the use of web searches and social media posts, instead of government and institutional websites, provides the potential for health misinformation about COVID-19 to be spread. This was particularly evident in some subdemographic groups, including participants under 29 years, single participants, participants without tertiary education, and males. These groups should be targeted with further education and preventative measures.

Acknowledgments
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Conflicts of Interest
None declared.

Multimedia Appendix 1
Technology use during COVID-19 lockdown survey. [DOCX File,22KB-Multimedia Appendix1][13]

Multimedia Appendix 2
Logistic regressions of technology use. [DOCX File, 20 KB-Multimedia Appendix 2][14]

Multimedia Appendix 3
Logistic regressions of COVID-19 knowledge. [DOCX File, 19 KB-Multimedia Appendix 3][15]

[13] https://jmir.org/api/download?alt_name=formative_v5i5e25273_app1.docx&filename=9d9f7d98dbb8d59c493511f56187a55b.docx
[14] https://jmir.org/api/download?alt_name=formative_v5i5e25273_app2.docx&filename=80f956bf8e61ff4d5b1029a243c77020.docx
[15] https://jmir.org/api/download?alt_name=formative_v5i5e25273_app3.docx&filename=dcd5a246868301959b9cb8b1b39bb826.docx

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Part 2. Digitally assisted HIV self-testing

CHAPTER 6. Evaluation of a mobile application to support HIV self-testing in Johannesburg, South Africa

This chapter is based on:

Gous N, Fischer AE, Rhagnath N, Phatsoane M, Majam M, Lalla-Edward ST. Evaluation of a mobile application to support HIV self-testing in Johannesburg, South Africa. S Afr J HIV Med. 2020;21(1):a1088. https:// doi.org/10.4102/sajhivmed. v21i1.1088

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Abstract

Background

HIV-self-testing (HIVST) reduces barriers associated with facility-based testing, however no formal mechanism exists for users to self-report results or link to care. The Aspect™ HIVST mobile application (app) was developed for use in South Africa.

Objectives

This pilot evaluated the acceptability and feasibility of the Aspect™ HIVST app for individuals from the inner-city of Johannesburg.

Method

This cross-sectional pilot, with a convenience sample of 300 adults was conducted in July 2018. Participants were provided an OraQuick HIVST kit and a smartphone preloaded with the app, then asked to follow the in-app instructions for use (IFU) to complete the HIVST and upload results. Trained healthcare workers (HCWs) observed and recorded any deviations from the IFU, and conducted a post-test survey to assess acceptability. Feasibility was evaluated as the number of participants that agreed to participate, completed the self-test, and uploaded all information onto the app correctly.

Results

Two-hundred and ninety six (98.7%) participants found the app easy to use, difficulties experienced were related to the IFU (26;8.7%). Participants suggested multimedia supplements (4;1.3%), additional languages (4;1.3%) and simplified instructions (5;1.7%) to reduce difficulties. All individuals approached agreed to participate, 267 (89.0%) correctly completed all steps and 210 (78.7%) successfully captured all information on the app. Most errors (26;8.7%) were testing errors and 1 (0.3%) was from the app-sequence. Twelve (4.5%) errors were with test strip imaging and 72 (27.0%) discordances with demographic information.

Conclusion

Despite some challenges with IFU interpretation and data capture via the app, this pilot showed that the Aspect™ HIVST app is an acceptable way to upload mobile HIVST results and demographic information to a central database.

Introduction

In 2012, the OraQuick ADVANCE Rapid HIV-1/2 Antibody Test (OraSure Technologies Inc, Bethlehem, USA) was the first HIV self-test (HIVST) approved for sale in the United States as an over-the-counter HIVST rapid diagnostic test (RDT) for individuals with no prior HIV testing experience [1]. Since then, over 2.5 million HIVST kits have been sold globally and more than 4 million have been distributed through donor funded programmes [2]. The World Health Organization (WHO) strongly recommends that HIVST be utilized as a way to complement existing HIV services [3] as self-testing may reduce barriers associated with traditional facility-based testing, like travel, wait times and privacy concerns [4,5].

Based on this growing body of evidence, South Africa became one of over 40 countries to have incorporated HIV self-testing into their national HIV policies [6,7], with self-testing introduced as a way to help close the gap between the 84.9% of adults living with HIV that know their HIV status and the 90% target of the UNAIDS 90-90-90 initiative [5,8-10]. The introduction of HIVST programmes will improve access to further HIV diagnostic services, prompting an increase in testing uptake and frequency, which could lead to earlier diagnosis [11].

There are, however, several concerns related to HIVST, as there is no formal pipeline for users to self-report their results or be linked to care following the self-test. These HIVST kits are not diagnostic, but rather considered tests for triage, and all positive results should prompt the user to seek confirmatory testing by a trained healthcare professional [12]. Furthermore, the independence of HIVST presents considerable challenges surrounding the monitoring and evaluation (M&E) of HIVST programmes, which are required by public health stakeholders to understand the uptake and effectiveness [13].

Strong mobile phone penetration in low- and middle-income countries (LMIC) [14,15] has led to the development of a variety of mobile health (mHealth) interventions to complement HIVST. These include telephone hotlines, short message service interventions, internet-based platforms and mobile applications (apps) [16-20]. A Brazilian study conducted in 2019 showed that an internet-based intervention targeting men who have sex with men led to 21.4% of online participants self-reporting, while an interactive voice response telephone line in South Africa was found to link 9.8% of participants to care [21]. While these platforms have shown varied success, the introduction of mHealth interventions for linkage to care and M&E are in line with the South African National Department of Health mHealth Strategy (2015) and should be explored further [22].

Despite data concerns in LMICs [23], recent trends are towards the development of downloadable apps due to their agility and scalability [24]. The app interface also provides

developers with a malleable platform that can be tailored to individual users, allowing them to curate a collection of HIVST information, resources and guidance for testers, while also capturing the HIVST result data [19,20]. Recently, HIVSmart™, a Canadian app, was developed to guide users through the testing process, link them to care, and store the HIVST result data. Preliminary evaluations in key Canadian populations, as well as healthcare workers in South Africa have shown the app to be feasible and acceptable, however neither HIVSmart™, nor any other apps, have been developed or tested for the general population in LMICs [9,20,25].

South Africa has shown previous acceptance of HIV-related mHealth interventions with SmartLink, an app that improved linkage to care for clinic-based HIV testing in participants under 30 years of age [26]. Another successful mHealth intervention, MomConnect, has been used by over 2 million pregnant South African women with information regarding their pregnancy, while also creating a national pregnancy registry [27,28].

The Aspect™ HIVST app, was developed to help strengthen and complement HIVST programmes by supporting self-testers through testing, facilitating linkage to care and digitizing the reporting of HIVST results through an operational dashboard for M&E. The specific objective of this pilot study was to evaluate the acceptability and feasibility of the Aspect™ HIVST app for individuals from the inner-city of Johannesburg, in order to advise further scale-up. We present the findings from this pilot.

Methods

Study Design

This evaluation was a cross-sectional pilot study that ran for four weeks in July 2018. A convenience sample of 300 consenting adults was recruited from inner-city Johannesburg, South Africa. Recruitment was based around the Hillbrow Health Clinic by CHWs that went into the surrounding communities and spoke to the public about the current study. Those interested were screened against inclusion/exclusion criteria, then brought to the Hillbrow Clinic to provide consent and complete the study. Participants were included if they owned a mobile phone (feature phones or higher for app compatibility) and could provide a valid mobile phone number, were 18 years or older, able to read English and able to provide written informed consent. Participants were excluded if they did not meet the inclusion criteria, were currently on a pre-exposure prophylaxis (PrEP) regime or any HIV treatment medication, could not provide valid identification or had any condition that may have interfered with the testing process (such as intoxication or poor vision).

Development of the Aspect™ HIVST mobile app

The Aspect™ HIVST app was designed for android and deployed by SystemOne, LLC (Northampton, MA, USA), a diagnostic connectivity and disease intelligence company. The Aspect™ HIVST app was designed to be integrated with the existing Aspect™ software platform, a system designed to integrate directly with diagnostic instruments in order to collect digital results for real-time monitoring and reporting via an operational dashboard. The Aspect™ API can also communicate with RedCap, an existing South African healthcare database, and this application is already in being used for reporting HIV viral load results and early infant HIV diagnosis (EID).

The Aspect™ HIVST app was developed using Dimagi Commcare (Washington, USA), a common data-gathering platform. The app was structured to allow the self-tester to collect their own demographic information, provide the tester with instructions on how to perform self-testing, input their interpretation of the test result, and capture a photo of the HIVST strip (Figure 1). Demographic data were collected with one question per page and included the self-testers age, gender, mobile number, education level and whether they had self-tested before. The instructions, which were developed in English, provided the tester with step-by-step guidance, presented pictorially with simple wording taken directly from the HIVST kit manufacturer's instruction sheet, so that self-testing could be performed independent of a clinical setting.

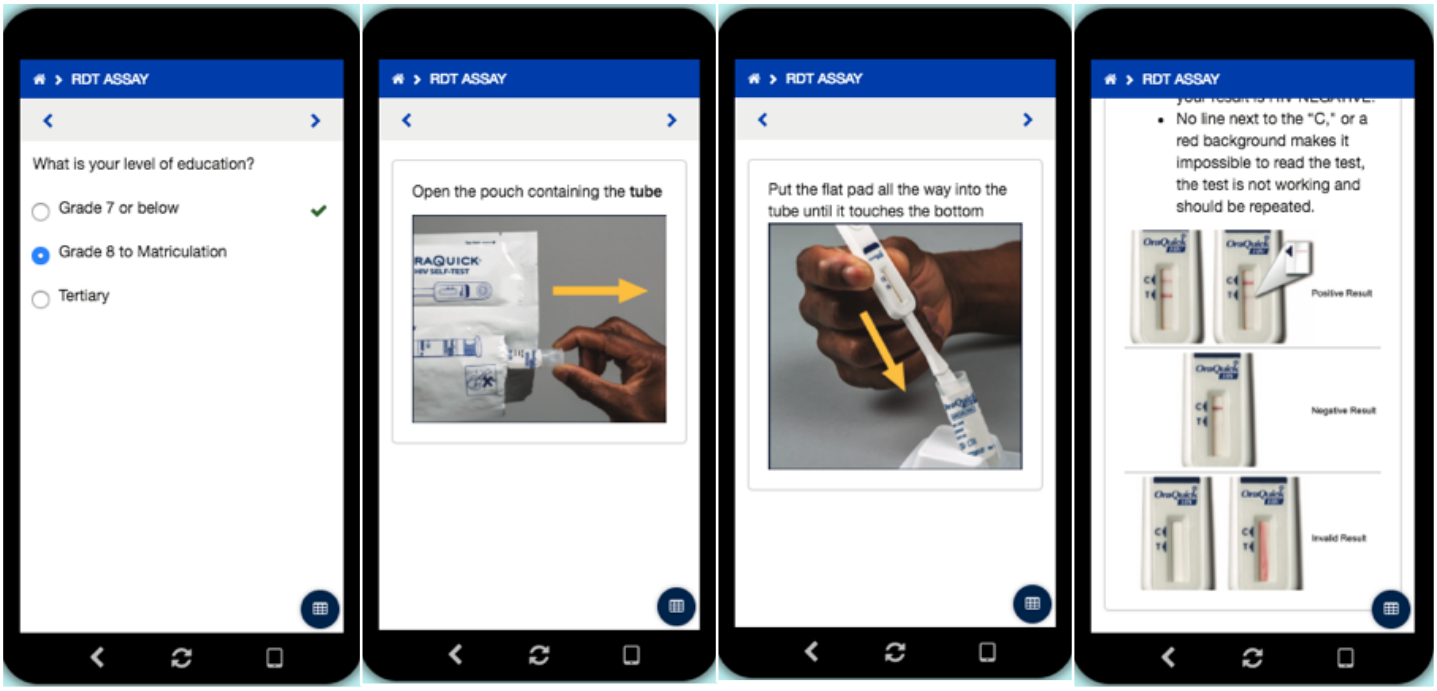

Figure 1. Screenshots of the Aspect™ HIVST mobile app

All data gathered by the app was automatically uploaded via a secure server to the Aspect™ data management platform for viewing and review by the research team. Data collected in Aspect™ was presented in aggregate form on a data dashboard that could be configured to display any relevant statistics for the research team. The app security was implemented with privacy by design methodology as per Protection of Personal Information (POPI) guidelines [29] with patient data encrypted in transit and at rest and also followed best practice guidelines in accordance with General Data Protection Regulation recommendations [30].

Data Collection

Trained healthcare workers (HCW) obtained voluntary informed consent from the participant in a private room, then uploaded the participant's unique study identification number on the app. Once uploaded, the participant was handed a Samsung J5 smartphone, preloaded with the Aspect™ HIVST app, and an accompanying HIVST kit. The sealed test kit contained an English brochure with instructions for use (IFU) as part of the standard packaging, however, the participant was requested to perform the HIVST by following the IFU included in the HIVST kit and the digital version of the IFU provided on the app. Obtaining the sample takes 5 to 8 minutes when using the IFU (either paper or digital), followed by a 20 minute incubation period. The OraQuick HIVST kit (Orasure Technologies Inc, Bethlehem, USA) was used for the study as it had already undergone full evaluation and was approved for use in South Africa [31]. In a private room at a clinic, participants were asked to navigate the app and perform the HIVST with no assistance, while the HCW observed the process and recorded any deviations from the app instructions. Following the test, the HCW asked the participant a number of questions to obtain feedback on the app design and willingness to use an app for HIVST in future.

After the 28-minute test was completed, the participant returned the phone to the HCW, who then uploaded their professional interpretation of the HIVST result on the app. Regardless of the HIVST result, the HCW performed confirmatory testing using a commercial HIV rapid test (Advanced Quality, InTec Products, Inc, Xiaman, China). If the participant's self-test and HCW confirmatory tests were discordant, a third test was performed (Abon 1/2/O Tri-line, Abon Biopharm Hangzhou Co.,Hangshou China). The HCW uploaded all results, as applicable, on the app for reporting purposes. Participants with HIV positive results (based on the confirmatory testing) were referred to a clinic as per standard of care [7].

Evaluation of HIVST and mobile app usage

Acceptability outcomes

The evaluation of mobile apps may provide challenges to researchers due to the nature of their varied users, objectives, interfaces and mobility [32]. In many cases, app developers and researchers develop data collection tools that are app-specific, in order to explore concepts

exclusive to their app [33,34]. For this pilot study, a survey was developed to advise preliminary scale-up of the app, which looked at general acceptability and asked a set of close-ended (yes/no) and open-ended questions, similar to the methodologies found in other mHealth app evaluations [21,35]. The survey collected participant demographic information and included questions on whether the app was easy to use; which steps, if any, were difficult to understand; would they use the app again; would they be willing to download this app in the future and if they had any suggestions to improve the app. The demographic information collected by the survey and recorded by the HCW was also used to reference the accuracy of data capture on the app.

Feasibility outcomes

Similar to acceptability, there is no universal measure for determining the feasibility of an app, however the generally accepted formula for feasibility includes three criteria; the participants' acceptance of using the app, the ability of the participant to complete tasks on the app and the ability of the app to perform the required tasks [36]. These variables inevitably change based on the functionality of the app and its intended users, and for this pilot the feasibility criteria were as follows:

1. User acceptance of app: The number of participants that agreed to use the app.
2. Successful test completion using app: The number of participants that completed the testing through the app without error (i.e. experiencing difficulties or asking the HCW for assistance).
3. Success of data capture through app: The number of participants that captured their demographic information (when compared to the original records collected by the HCW), uploaded their interpreted test result and captured their test-strip images correctly.

The final feasibility score is then presented as a percentage of the final criteria [36].

Data analysis

All data extracted from the survey questionnaire (paper based) was entered into an access controlled excel spreadsheet. The quantitative data captured on Aspect^{TM} were extracted into a separate access controlled excel spreadsheet. Quality control checks involved a 10% randomized check comparing paper based tools against data on the spreadsheet. This was performed by the quality control officer on a daily basis. All data was coded then exported to Stata version 15.1 (StataCorp, USA) for descriptive analysis. Data were grouped into categories to define demographic characteristics, then presented as frequency counts and percentages.

Ethical Consideration and approval

Ethics approval was obtained from the University Human Research Ethics Committee (reference number 180504). All participants provided written informed consent and were compensated ZAR150 for their time.

Results

Demographics

Of the 300 participants, over two thirds (211; 70.3%) were younger than 36 years old, there were 134 (44.7%) female participants, and 231 (77.0%) participants were educated up to at least high school level. Only 35 (11.7%) participants indicated they had previously self-tested. This information is presented in Table 1.

Table 1. Demographic characteristics.

Demographic	Frequency	Percentage (%)
Sample size	300	100.0
Age		
18-25 years old	105	35.0
26-35 years old	106	35.3
Over 35 years old	89	29.7
Sex		
Female	134	44.7
Male	166	55.3
Highest level of education		
Grade 7 or less	18	6.0
Grade 8 to matric	213	71.0
Tertiary school	69	23.0
Ever self-tested before		
Yes	35	11.7
No	265	88.3

HIV test outcomes

Forty-two (14.0%) participants interpreted their self-test result as HIV positive, however there were 5 (1.7%) discordant interpretations between participants and HCWs (Table 2). Three (1.0%) results were interpreted as positive by the HCW but either invalid (1; 0.3%) or negative (2; 0.7%) by the participant, and 2 (0.7%) results were interpreted as negative by the HCW but interpreted as either indeterminate (1; 0.3%) or positive (1; 0.3%) by the participant. Manual review of these discordant test result images on the Aspect™ dashboard by a senior researcher confirmed the HCW interpretation in all discordances. The confirmatory testing of all participants conclusively diagnosed 43 (14.3%) as HIV positive, all of whom were referred to care by the HCW.

Table 2. HIV testing outcomes.

HIV test results	Frequency	Percentage (%)
Sample size	300	100.0
HIVST- participant interpretation		
HIV positive	42	14.0
HIV negative	253	84.3
Invalid	5	1.7
HIVST- HCW interpretation		
HIV positive	43	14.3
HIV negative	254	84.7
Invalid	3	1.0
Interpretation Discordance		
Correctly interpreted	295	98.3
Interpretation error	5	1.7
HIV confirmatory testing		
HIV positive	43	14.3
HIV negative	257	85.7

Acceptability

Nearly all participants (296/300; 98.7%) found the Aspect^{TM} HIVST app easy to use, when surveyed, however 26 (8.7%) participants experienced some difficulty working through the testing steps as outlined in the app (Table 3). Almost all of the difficulties were related to the self-testing procedures, as 18 (6.0%) participants had difficulty sliding the tube into the stand, eight (2.7%) had difficulties swabbing their gums and three (1.0%) stated that the instructions were not clear. Another four (1.3%) participants had difficulty taking and uploading the picture of the test to the app. When asked for suggestions to make the app easier to use, five (1.7%) participants recommended that the instructions and steps be clarified, while four (1.3%) participants specifically suggested adding a multimedia component to the instructions. Another four (1.3%) participants suggested that the app be available in local languages and two (0.7%) participants stated that the phone memory requirements should be decreased. All but one (299/300; 99.7%) participant was willing to use the app again and only two (0.7%) participants stated that they would not be willing to download the app in the future.

Table 3. Acceptability outcomes.

Question	Frequency	Percentage
Sample Size	300	100
Did you find the mobile App easy to use?		
Yes	296	98.7
No	4	1.3
What steps in the App did you find difficult to understand or follow,		
Sliding the tube into the stand	18	6.0
Swabbing the gums	8	2.7
Taking/saving the picture	4	1.3
Instructions were not clear	3	1.0
No difficulties	274	91.3
If you choose to self-test again, would you be willing to use the App again to help guide you?		
Yes	299	99.7
No	1	0.3
If you choose to self-test again, would you be willing to download the App to your own mobile phone		
Yes	298	99.3
No	2	0.7
Do you have suggestions on how to make this App easier to use?*		
Add voice/video notes	4	1.3
Add local languages	4	1.3
Clarification of instructions and steps	5	1.7
Decrease phone memory requirements	2	0.7
No suggestions	285	95.0

*Values may not add up to 100% as variables are not mutually exclusive.

Feasibility

The final feasibility score was 70.0%. All 300 individuals approached for this study agreed to participate in the evaluation of the Aspect^{TM} HIVST app (Table 4). Of the 300 participants, 267 (89.0%) successfully completed the HIVST by following all of the steps on the app without error. The majority of errors (26; 8.7%) came from participants performing the testing procedures incorrectly, after reading the instructions on the app, which included sliding the tube into the stand (18; 6.0%) and swabbing the gums (8; 2.7%). Another four (1.3%) participants had difficulties with the language of the instructions, while eight (2.7%) participants made errors interpreting their HIVST results and one participant (0.3%) could not properly navigate the pages of the app.

Of the 267 participants that completed the testing, 210 (78.7%) participants successfully captured all information on the app. The most erroneous variable was previous testing history, where 34 (12.7%) participants submitted information that did not correlate with what they stated to the HCW during the survey. The variables age and highest level of education each had 12 (4.5%) participants that exhibited discordance and there were also two (0.7%) discordances with gender compared with HCW-recorded data. Twelve (4.5%) participants also uploaded an illegible image of the HIVST strip to the app.

Table 4. Feasibility outcomes.

Feasibility criteria	Sample size	Frequency	Percentage (%)
Agreed to use the app	300		
No		0	0.0
Yes		300	100.0
Successfully completed the test using app*	300		
App errors		1	0.3
Testing errors		26	8.7
Language errors		4	1.3
HIVST interpretation errors		8	2.7
Successful completion		267	89.0
Successfully captured all information on app?*	267		
Age discordance		12	4.5
Gender discordance		2	0.7
Education discordance		12	4.5
Previous test discordance		34	12.7
illegible image captured		12	4.5
Successful upload		210	78.7
Feasibility	300	210	**70.0**

*Values may not add up to 100% as variables are not mutually exclusive.

Discussion

This pilot study is the first investigation of an mHealth app to enhance monitoring and evaluation of HIVSTs for individuals from the inner-city of Johannesburg, and the findings from this pilot have established that participants showed high acceptability of the intervention, while also identifying challenges that can be targeted for improvement as the platform scales up. The high acceptability was similar to that of the HIVSmart™ app and a Brazilian internet-based intervention, however these studies only evaluated the feasibility of using the app to link patients to care or increase testing uptake, respectively [9,20,21,36].

The Aspect™ HIVST app, instead, aimed to guide participants through the testing process, then upload the results to a central server for M&E, and this additional layer of complexity has introduced more opportunities for user error. The majority of errors, however, were not as a result of the app functionality, but rather test usability and the IFU that guided the self-testing process. Errors stemming from the IFUs have been well documented in a number of HIVST studies, including ones from South Africa [37-39]. Suggestions like clarifying the instructions, incorporating video or voice notes, and offering additional languages should all be taken into consideration, especially as more HIVSTs, each with specific IFUs, become available to market. Some of these suggestions have already been implemented by other platforms, as the HIVSmart™ app is already available in both of Canada's national languages and provides supplemental video content [20].

There were a number of discrepancies between HCW-recorded and app captured data on participant demographic information. There were also some difficulties in the uploading of the test strip photo via the app. A simple summary page, similar to that seen on a banking app before completing a transaction, could provide the user with an opportunity to review their information before submitting it through the app. This additional checkpoint should help prevent any data entry errors. One variable however, previous HIV testing history, had 34 (12.7%) discordant entries between what the HCW recorded and what the app captured; all 34 reported as never having HIV tested to the HCW, but were captured in the app as having previously tested. It is possible that privacy of the app has revealed an interviewer bias, where some participants may not have felt comfortable sharing sensitive information with the HCW, but felt free to do so through the app. Previous mHealth studies have also found that self-administered tools may decrease interview bias [40], however further evaluation of this app and its users would be required before stating that the app is responsible for removing or decreasing this interviewer bias.

Some participants also had difficulty understanding how to take a picture of the test strip. When test images were reviewed on the Aspect™ dashboard, the images were quite variable in terms of quality. The purpose of this functionality was to allow a third party to manually review test images and flag potential discordant results for follow-up. However, similarly to other studies [20,41], we had high concordance between participant and HCW interpretation of the self-test and thus this step may not even be necessary if lay persons are able to interpret results as accurately as trained HCWs. In low bandwidth environments, the requirement to upload images may also incur additional data charges and may not be cost effective.

With the number of countries adopting HIVST policies on the rise, the M&E of these programmes poses a unique set of challenges [12] and measurement of uptake and effectiveness becomes difficult. The Aspect™ HIVST app facilitated the capture of HIVST data directly to an operational dashboard, namely Aspect™. This dashboard was developed by SystemOne and is currently being used to report Tuberculosis and HIV viral load results from over 3000 diagnostic instruments across 43 countries [42]. For this study, the dashboard displayed very basic summary HIV statistics, a list of individual test results and also supported the downloading of automated reports. This could allow a programme manager to remotely monitor indicators such as uptake, demographics of the testing population, HIV positivity rates, invalid rates and improve reporting against key performance indicators. The functionality of the dashboard also allows pushing of automated SMS notifications directly to the tester based on their HIV result, which could be used to promote confirmatory testing and help link them to care [43].This is especially important for HIVST, as one of the problems with home testing is that people receiving a positive diagnosis are suddenly faced with a serious diagnosis and no immediate access to information, counseling or treatment resources [11]. The feasibility of these dashboard features should be considered for future research.

Data concerns are also an important issue in South Africa, with previous mHealth studies highlighting data costs and phone memory as a barrier to entry [26,44]. Future app development should focus on keeping storage requirements minimal to ensure that the app is available for as many individuals as possible. Furthermore, the necessity to upload images may also incur additional data charges and may not be affordable for all users.

Limitations

The study had several limitations. Convenience sampling from one sub-district from inner-city Johannesburg was used to recruit participants limiting the generalizability of the findings, and the compensation of participants may have accounted for the very high participation rate. Furthermore, the majority of participants were under 35 years old, which may have made it easier for them to navigate a mobile app as they may be more tech-savvy than older age groups. The Aspect™ HIVST app was only available in English. It was also only tested on a Samsung phone, and it may not reflect the usability of the app on other phones owned by the general population, especially across different operating systems and memory capacity. The discordance between HCW-recorded and app-captured demographics may reflect an interviewer bias, while the process of testing in front of a HCW may have increased the number of forced errors due to the pressures of being observed. Performing the HIVST with the app in a clinic, with a HCW present, may also present bias, as the app is intended to be used independent of a clinic setting. Another limitation of the pilot process was that the HCWs did not record the participants' interpretation on paper so results discordance could be verified as was done for the other variables.

Although recent studies have introduced validated data collection tools for mHealth usability [45], at the time of this study, there were also no validated data collection tools to measure the acceptability and feasibility of mHealth apps for HIVST, so the study-specific questions may not be used to reproduce these results in similar settings. Similarly, the use of only one HIVST kit and its accompanying IFU means that these results cannot be generalized across all HIVSTs, especially since many of the errors were related to the interpretation of the IFU.

Conclusions

With millions of HIVST kits distributed worldwide without adequate tracking, the need for M&E of these kits is ever increasing. On an individual level, this may lead to better linkage to care and follow-up with patients, and on a national level, tracking can identify areas of need to optimize kit distribution, marketing and supplementary information. Despite some challenges with IFU interpretation and data capture via the app, this pilot study has shown that the Aspect^{TM} HIVST app is an acceptable way to upload mobile HIVST results and demographic information to a central database.

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CHAPTER 7. Uptake of the Ithaka mobile application in Johannesburg, South Africa, for human immunodeficiency virus self-testing result reporting

This chapter is based on:

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Abstract

Background

HIV self-testing (HIVST) can reduce facility-based HIV testing barriers, however no proven applications exists with widespread uptake for self-reporting or linkage to care. Mobile health(mHealth) applications(apps) have shown high usability and feasibility scores, but none have evaluated the reporting results as an outcome. Ithaka was developed for South Africans to self-report HIVST results outside clinical settings.

Objectives

This study investigated the use of Ithaka as a support tool for HIVST users, specifically the ability to self-report results.

Method

This cross-sectional study ran from November 2018-June 2019. At existing HIVST distribution sites, individuals were given HIVST kits, then invited to log into a reverse-billed app. Participants could test at home and report their results through the app anytime. The app tracked when people logged-on, registered, received counselling and reported results. Post-study surveys on user experience were also conducted.

Results

Of 751 participants, 531(70.7%) logged onto the app, 412(54.9%) registered, 295(39.3%) received counselling and 168(22.4%) self-reported results. Participants strongly agreed that Ithaka was useful and easy to use, but agreed that it was easy to upload results. All participants were invited to complete the post-test survey via telephone, but only 41 completed the survey, and 39/41(95.1%) completed the app journey, while 2/41(4.9%) were unable to upload results. All (41/41;100.0%) respondents would recommend the app and most (36/41;87.8%) had no challenges, although 2/41(4.9%) cited perceived data costs, 2/41(4.9%) had difficulty uploading results, and 1/41(2.4%) had language challenges.

Conclusion

Despite the small sample size, this study has shown that HIVST participants in real-world conditions were willing and able to self-report results via the app, while also identifying areas of improvement for scaling up.

Background

HIV Self-testing (HIVST) can reduce barriers associated with conventional facility based HIV testing, and since their introduction in 2012, more than 6.5 million HIVST kits have been distributed globally [1,2]. In 2018, South Africa integrated HIVST into their national HIV strategy as a way to expand testing beyond standard healthcare facilities, in order to meet the UNAIDS 90-90-90 target [3,4]. These targets state that 90%, 81% and 73% of the total population should know their HIV status, be linked to antiretroviral treatment (ART) and experience viral suppression, respectively [5]. Despite the benefits of HIVST, there are some gaps associated with their use, as they are hard to track and are only classified as tests for triage, which should not be considered diagnostic [6]. Furthermore, South Africa does not have an appropriate system for users to self-report their results, or be linked to care, and this lack of reporting makes it difficult for public health stakeholders to conduct monitoring and evaluation on the uptake and effectiveness of HIVST, especially at the population level [7].

Over the last decade, low- and middle-income countries have experienced an increase in mobile coverage and smartphone use, which has qualified the introduction of mobile health (mHealth) interventions in these regions [8-10]. There is a strong body of evidence supporting the use of mHealth interventions, to enhance patient outcomes for a broad spectrum of health conditions, including HIV. In low-income settings specifically, different interventions have targeted various stages of the HIV care cascade, including text message campaigns, telephone hotlines and mobile applications (apps) [6, 11-14].

South Africa has been investigating the use of mHealth interventions to accompany HIVST, for users to self-report their results, and in a recent study, 9.8% of participants self-reported their results using an interactive voice response telephone hotline [15]. Feasibility studies have also been done on the HIVSmart! app and the AspectTM app, both mobile apps that guide self-testers through the testing and reporting process. These apps were both tested in a clinical setting, under the observation of healthcare workers (HCWs), and while both apps reported high usability and acceptability, they did not investigate the reporting of results in a non-clinical setting as an outcome [16-19].

The Ithaka app (Aviro Health; Cape Town, South Africa) has been developed to close this gap by providing untrained HIVST users a mobile platform to self-report their HIVST results independent of a formal clinical setting, while also removing the potential for observational bias. The objective of this study was to investigate the use of Ithaka as an HIVST support tool for individuals, specifically the ability to report self-results outside a clinical environment.

Methods

Study Design

This was a cross-sectional evaluation conducted from November 2018 until June 2019, with a random sample of 751 consenting adults from the general population of inner-city Johannesburg, South Africa. People who received an HIV self- test kit were invited to participate in the study. As per the HIV self-testing programme, requirements to receive an HIVST kit were wanting to perform an HIVST, had not tested for HIV in the previous 3 months, had a mobile phone compatible with the app, were 18 years or older, able to read English and able to provide written informed consent. Participants were excluded if they were known HIV positive, were a practicing HCW or if they were taking drugs that could affect the sensitivity of the test, like pre-exposure prophylaxis, ART or an experimental HIV vaccine. Before the study, a two-week pilot period that included 41 people, was used to improve operational issues, refine the content and user experience of the app, and confirm the linkage between the data collection and data analysis datasets.

App Development

The Ithaka self-test support tool is a mobile phone-based tool to support users through self-testing and eventual confirmatory testing. It is a Progressive Web App (PWA), which is accessible as a reverse-billed mobi-site, where the provider pays any data costs, rendering the tool free to end users. The Ithaka platform provides users with a tailored journey to encourage user retention, reporting and linkage to care, as well as gamification to boost user engagement. Ithaka guides the patient through the various testing steps and will prompt the user to report back on their status, progress, emotional state, information comprehension, and user satisfaction. Before conducting the self-test, users must complete a brief counselling component that explains the test process, and what to expect after obtaining the results, however, if users want more information, they can access integrated chat-based help at any time, or request a call back from a call center. In the event of a positive HIV result, the study participant is referred for clinical treatment and care, while participants that test negative will be counselled and encouraged to seek confirmatory testing at 3 months.

The Ithaka platform is secure, with unique user profile logins and encrypted back-end databases to ensure data security and patient anonymity in-line with Protection of Personal Information (POPI) guidelines [20]. Furthermore, stakeholders can receive real-time data on how users are engaging with the materials and platform. Screenshots of Ithaka are presented in Figure 1.

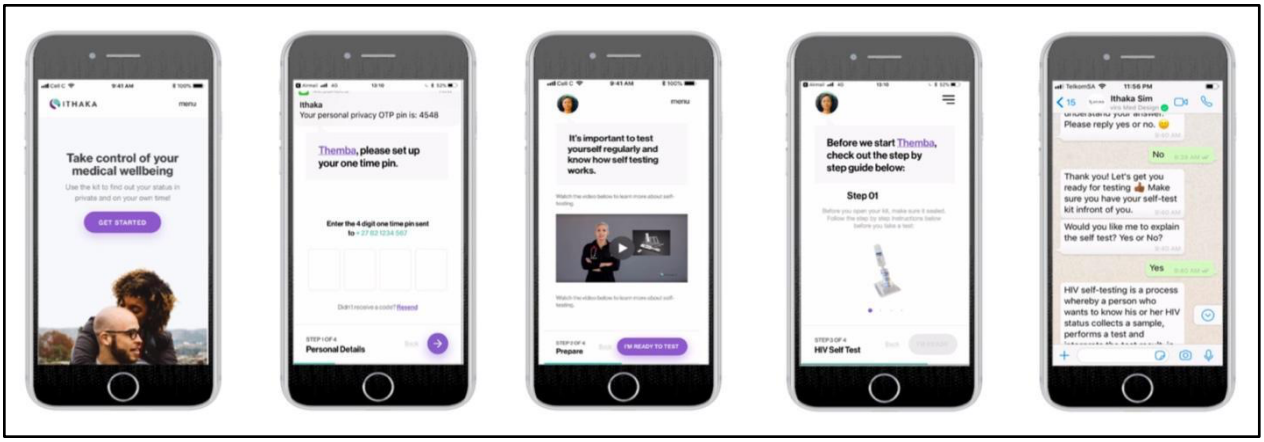

Figure 1. Ithaka screenshots

Data collection

HIV Self-Testing Africa (HSTAR) is a HIVST distribution and research programme that supplies free OraQuick® Rapid HIV Self-Test (Orasure Technologies; Bethleham, USA) to people in Region F of Johannesburg, South Africa, through fixed point distribution sites, and these sites were used to recruit participants for the Ithaka study as well. In order to collect a random sample and minimise disruption to the regular HSTAR programme (since recruitment was being done by the distribution team), one random day each week was used to recruit participants for the Ithaka study. After an individual received their self-test, peer educators invited them to participate in the Ithaka study. No additional log was maintained to document individuals that declined to participate.

If an individual showed interest, the peer educator provided detailed information on the Ithaka study and obtained a written informed consent prior to administering the pre-survey questionnaire. The peer educator helped the participant log into and register on the app on the participant's phone, which was available through a URL.

Data was collected from three sources as follows:

1. **Pre-study survey**. An in-person survey was conducted by peer educators to capture demographic information including age, education, shared phone, gender and location.
2. **Ithaka platform**. The app tracked user engagement marked by logging on, registering, receiving counselling and reporting results.
3. **Post-study survey**. A telephone survey was conducted to obtain user feedback on the app, which included Likert scale questions ((1) Strongly disagree; (2) Disagree; (3) Neither agree nor disagree; (4) Agree; (5) Strongly agree) and open-ended questions. The Likert scale was used to understand the user experience of Ithaka (asking ratings on usefulness, ease of use, empowering, trustworthiness, ease of understanding, and reliability), and

whether it decreased barriers to report results, finding a clinic, read frequently asked questions, get reminders and make referrals. Participants were asked open-ended questions regarding their discontinued usage of the app, challenges using the app and if they would recommend it to a friend (Appendix 1). All participants were invited to participate in the post-study survey via a phone call to the number they had provided. Participants were eligible to participate if they provided consent and had completed the app journey, making it to the final reporting results stage, and answered all survey questions.

Data analysis

Data from the surveys and Ithaka database were cleaned in Excel (Microsoft; Seattle, USA), then exported to Stata V.14 (StataCorp; College Station, USA) for analysis. Demographic information and questions about app usage were described with frequency and percentages. User flow through the app was tracked then presented with frequency and percentage through each stage. Likert scores were averaged and presented as a number between 1 and 5, with numbers approaching 5 representing favourable outcomes.

Ethical Consideration and approval

Ethics approval was obtained from the Human Research Ethics Committee of a South African university (reference number 180708). All participants provided written informed consent. The app was made available as a reverse-billed site so participants did not incur data costs, but participants were provided no reimbursements for their time in the study.

Results

Demographics

A total of 751 people participated in the study. Nearly half of the participants (340; 45.3%) were between the ages of 26 and 35 years old, while a third were 25 years old or below (231; 30.8%) and about a quarter above 35 years of age (175; 23.3%). Four hundred and thirty-one (57.4%) participants were female, and 634 (84.4%) did not share mobile phones with anyone. Only 3 (0.4%) participants had a primary school education, while 444 (59.1%) had a secondary school education and 203 (27.0%) had a tertiary school education, or higher. The complete demographic characteristics are presented in Table 1.

Table 1. Demographic characteristics.

Demographic	Frequency (n=751)	Percentage*
Age		
18 - 25 years old	231	30.8
26 - 35 years old	339	45.1
Over 35 years old	175	23.3
Not answered	6	0.8
Sex		
Female	431	57.4
Male	318	42.3
Not answered	2	0.3
Highest level of education		
None	4	0.5
Primary school education	3	0.4
Secondary school education	444	59.1
Tertiary school education	203	27.0
Not answered education	97	12.9
Do you share a phone?		
No	634	84.4
Yes	74	9.9
Not answered	43	5.7

Abbreviation: n, number

Note: *The percentages may not add up to 100.0% due to rounding.

Ithaka use

Figure 2 presents the cascade of Ithaka use from the point of enrollment to reporting HIV results. Approximately three quarters (531; 70.7%) logged on to the app. More than half (412; 54.9%) the enrolled participants completed the registration process, 295 (39.3%) enrolled participants completed the pre-test counselling and the how-to-test instructions, and 168 (22.4%) enrolled participants self-reported their results. Of the 168 participants that self-reported their results, 14 (8.3%) reported as HIV positive.

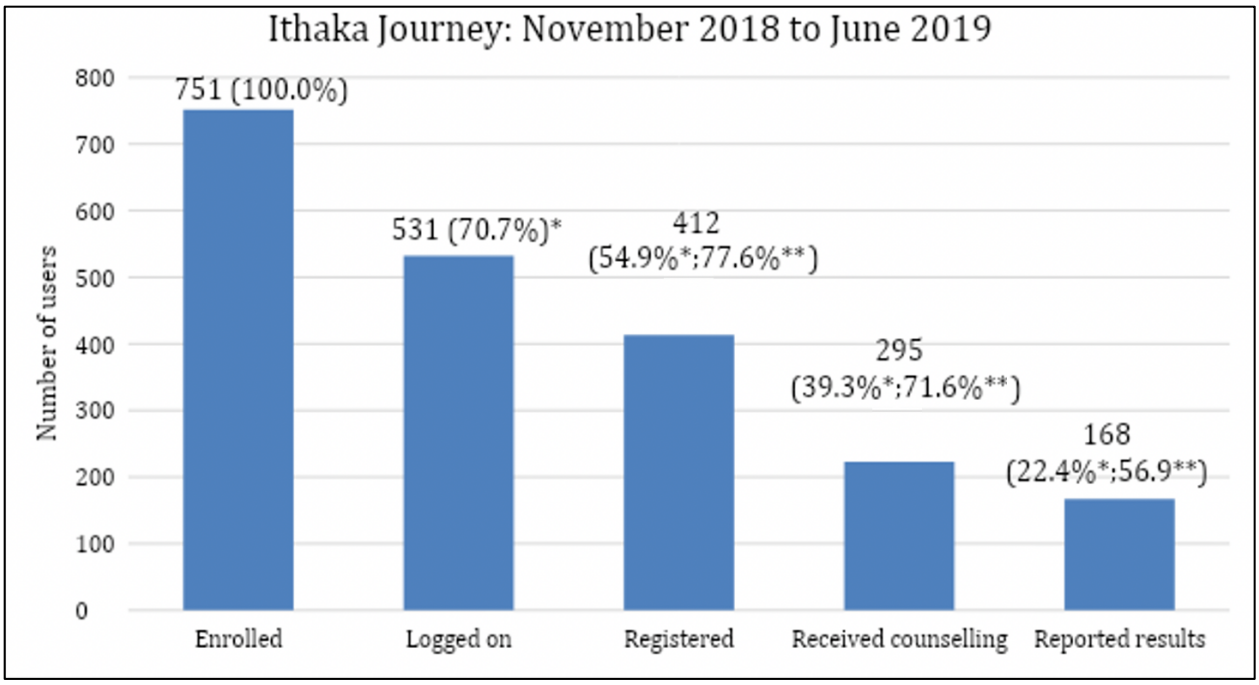

Figure 2. User journey through Ithaka

Notes: * percentages calculated using 751 as the denominator; ** percentages calculated using the previous number in the cascade as the denominator

Ithaka user experience

Of the 336 participants that were successfully contacted for the post-test telephone survey, consent to participate was provided by 190 (56.5%) participants, although only 112 (33.3%) were eligible for the post-study survey, and 41 (37.3%) completed the entire survey. In order to quantify the user experience, mean Likert scores approaching 5 represented strong agreement with the statement, whereas scores approaching 1 represented strong disagreement with the statement. The two statements, *Ithaka made it easy to upload results* and *Ithaka made it easy to find a clinic* had mean Likert scores of 3.8 (SD= 1.6) and 4.2 (SD= 0.9), respectively. All other user experience statements were strongly agreed with, receiving ratings that were above or equal to 4.5 (SD= 0.5-0.7). The mean Likert scores are presented with standard deviations (SDs) in Table 2.

Table 2. Mean Likert scores for user experience

Outcome	Mean Likert Score (n=41)	SD
Overall, Ithaka was useful	4.7	0.6
Overall, Ithaka easy to use	4.7	0.6
Overall, Ithaka made you feel enabled	4.7	0.6
Overall, you trusted Ithaka	4.7	0.5
Ithaka made it easy to upload results	3.8	1.6

Ithaka made it easy to find a clinic	4.2	0.9
The app language was easy to understand	4.6	0.5
The information in the app was reliable	4.6	0.7
The FAQs were helpful	4.5	0.7
The reminder and referral functions were useful	4.5	0.6

Abbreviations: n, sample size; SD, standard deviation; FAQ, frequently asked questions

When participants were asked why they had stopped using the app, 39/41 (95.1%) respondents stated that they used the app to completion, while 2 (4.9%) stated that they stopped because they were unable to upload their HIVST results. All (41/41; 100.0%) participants who responded stated that they would recommend the app to someone else, with respondents citing ease of use (12/41; 29.3%), liking the app (4/41; 9.8%) and privacy (2/41; 4.9%) as the main reasons for why they would recommend it to someone else. Most of the respondents (36/41; 87.8%) stated that they did not experience any challenges or difficulties while using the app, however 2/41 (4.9%) respondents cited data costs as a challenge, 2/41 (4.9%) respondents stated that they had difficulty uploading results, and 1/41 (2.4%) respondent stated that they had experienced challenges due to the app languages.

Table 3. Open ended user experience questions

Question	Frequency	Percentage
Why did you stop using the app? (n=41)		
Completed the survey at the end	39	95.1
Failed to upload results	2	4.9
Would you recommend this app to someone else? (n=41)		
Yes	41	100.0
No	0	0.0
Why would you recommend this app to someone else? (n=41)		
Easy to use	12	29.3
Liked the app	4	9.8
Privacy	2	4.9
Provides education	1	2.4
Language easy to understand	1	2.4
Reliable	1	2.4
Low data cost	1	2.4
No specific reason	19	46.3
What was the biggest challenge to using the app? (n=41)		
No challenge	36	87.8
Language	1	2.4
Data costs	2	4.9

Uploading results	2	4.9

Abbreviation: n, number

Note: *Percentages may not add up to 100.0% due to rounding.

Discussion

To our knowledge, this is the first study in South Africa to evaluate the use of an mHealth app to self-report HIVST results as an outcome, independent of observation in a clinical setting. Previous feasibility studies have shown high acceptance of mHealth apps for the monitoring and evaluation of HIVSTs, however, they only evaluated usability in the presence of HCWs and did not evaluate any reporting outcomes through the app [16-19]. Similar to these previous studies, the Ithaka app showed high self-reported usability among those interviewed, while also confirming that participants in real-world conditions were willing and able to self-report their results via the app. The self-reporting of results by logged on participants, through the Ithaka app was 22.4%, which is acceptable, considering that it is common for apps to lose up to 80% of their active users in the first week [21]. Furthermore, the percentage of HIVST results reported through Ithaka were more than twice that of a previous tele-health intervention in South Africa, which only led to 9.8% of participants self-reporting [15].

Despite this increase in self-reporting and high usability Likert scores, 43.1% of participants that received counselling (a proxy for completing the self-test) still did not self-report their HIVST results, which leaves opportunity for improvement. Although field testing of Ithaka followed a three month human centred design (including personal and journey mapping) and a two week pilot testing, a percentage (12.2%) of surveyed participants did experience challenges with the Ithaka platform. This not only suggests that users may need more than a brief introduction from a peer educator but that the technology development phase requires several iterations with greater consideration for pragmatic value propositions and testing of varied content/messaging before inclusion. Going forward, focus groups or follow-up interviews with participants that did not complete the app journey, could be done to further identify areas of improvement that caused participants to cease activity on the app.

Similar to reports of other South African digital health interventions, for users to completely embrace Ithaka and realize its' full use, marketing campaigns can be used to create awareness, followed by a more comprehensive onboarding to motivate users [22]. Although practical reasons for stopping use of the app, such as forgetting to log back in or not using the test yet, should be mitigated with text message reminders, which have been shown to improve the user responsiveness of other mHealth apps [23-25], we did not find this in our study in which registered participants received reminder messages on day 1 and day 7. Some participants cited data costs and network issues as challenges to the app, and these are well-documented barriers

to entry for any mHealth app entering the South African market [6,22], however Ithaka was a reverse-billed online platform that removed the barrier of data costs. As a reverse-billed platform, any and all data costs for using the platform are paid for by the service provider (Ithaka), and the end-user does not incur any costs, nor do they use any of their own data while on the platform. There may have been some confusion by study participants as to the meaning of reverse-billing, and this beneficial feature should be sufficiently explained to users in the future, so they know that no costs are incurred on their end while using the platform.

In South Africa, there is currently no endorsed platform for users to self-report their HIVST results, or be linked to care following a positive test [6], which makes the monitoring and evaluation very ineffective for the government and associated public health stakeholders [7]. This study has shown that as a proof-of-concept, HIVST users are willing and able to self-report their HIVST results via the Ithaka app, and this sharing of information on a national scale could greatly improve HIVST monitoring and evaluation.

While this study focused on self-testing, which directly addresses the gap between the first 90 and the 85% of HIV positive South Africans that know their status, it does not address the country's largest deficit, as only 71% of people that are eligible for ART are actively receiving treatment [26]. Ithaka could continue to increase active users by sending out reminders to encourage the self-reporting of results, and keep users engaged by promoting linkage to care opportunities. To improve accessibility and usability, The Ithaka platform has since been extended to WhatsApp and to support blood-based tests. The Ithaka platform has also undergone a number of process and content changes that were implemented as a way to continue improving on the HIVST reporting rate. In addition, extensions to the tool to support and confirm linkages to care and improve initiation and viral load suppression are currently undergoing piloting and development.

Limitations

This study presented some limitations. Participants were recruited through existing HIVST distribution points, so individuals may have had previous exposure to HIVST studies, and potential study fatigue may have influenced their willingness to participate. Due to this exposure, participants may have a greater base level background knowledge of HIVST than the general population. The Ithaka app was only available to individuals with mobile phones capable of running the current iteration of the app, and does not include individuals that could not access the app due to different operating systems or memory capacity. Furthermore, a peer educator helped participants log into and register on the app, which may have influenced the ease of use and initial components of the cascade.

The use of only one HIVST kit means that these results also cannot be generalized across all HIVST kits. Additionally, only 8.3% of participants self-reported a HIV positive result, which is much lower than the national prevalence of 13.1% and this may be due to a selection or reporting bias, where individuals that may be HIV positive did not participate, or report their positive results. The views presented of the user experience responses may not represent the views of the study population as only participants that completed the app journey and answered all questions were included in the post-study survey results. The low completion rate for some of the survey questions represents a minority of the group and a larger minority in relation to the general population. Lastly, the post-test survey was conducted via voice call, which may have attributed to this low completion rate.

Conclusion

Millions of HIVST kits have been distributed globally, however, there is currently no universally accepted platform for users to self-report their HIVST results, health behavior and outcomes in line with the HIV care cascade. This study has shown that HIVST users outside the clinical setting were willing and able to self-report their results via the app. This could be used on a national level to improve the monitoring and reporting of HIVST programs, leading to the optimization of kit distribution, and targeted marketing and support. The use of an app introduces the possibility to promote and improve linkage to care, counselling and follow-up for newly tested HIV positive users. This, together with exploring other popular channels for making digital services available such as WhatsApp, needs to be explored further to ultimately enable the development of an app that is user friendly, cost efficient and beneficial to HIV programs.

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Competing interests

LS and MA work for Aviro health and were involved in the design of the Ithaka HIVST app.

Author contributions

LS, MA, NR, MP and MM designed the study. LS, MA, NR and MP collected data, LS, NR, MP, STLE and AEF were involved in the data cleaning and analysis, AEF, STL-E, MP and LS wrote the initial draft of the manuscript. All authors critically reviewed and approved the final draft.

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Appendix 1. Post-study survey

Follow- up recruitment telephone survey To be completed at the end of the study by all participants that consent to the post-study survey and have completed the app journey (logging on, registering, receiving counselling and reporting results.)		
1	Are you willing to answer a few questions about the app you received?	Y/N (if no, end survey)
2	Why did you stop using the app?	❑ Completed the survey at the end ❑ Did not find it useful ❑ Did not enjoy using it ❑ Did not understand why I would use it ❑ Forgot to log back in ❑ Other (please explain): _____
3	Overall, the tool is useful	Likert scale (*1 Strongly disagree 2 Disagree 3 Neutral 4 Agree 5 Strongly agree)
4	Overall, the tool is easy to use	Likert scale
5	Overall, the tool made you feel enabled	Likert scale
6	Overall, you trusted the tool	Likert scale
7	The tool made it easy to upload results	Likert scale
8	The tool made it easy to find a clinic	Likert scale
9	The app language was easy to understand	Likert scale
10	The information in the app was reliable	Likert scale
11	The FAQs were helpful	Likert scale
12	The reminder and referral functions were useful	Likert scale
13	Would you recommend this app to someone else:	Y / N
14	Reason why? **(*If No N/A)**:	
15	The biggest challenge to using the app for me was:	❑ language ❑ data costs ❑ no phone ❑ usefulness ❑ other (specify): _____

CHAPTER 8. Digitally supported HIV self-testing increases facility-based HIV testing capacity in Ekurhuleni, South Africa

This chapter is based on:

Mshweshwe-Pakela NT, Mabuto T, Shankland L, Fischer A, Tsukudu D, Hoffmann CJ. Digitally supported HIV self- testing increases facility-based HIV testing capacity in Ekurhuleni, South Africa. S Afr J HIV Med. 2022;23(1), a1352. https://doi. org/10.4102/sajhivmed.v23i1.1352

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Abstract

Background

HIV testing is the first step for linkage to HIV prevention or treatment services. Facility-based HIV testing is the most utilised method, but faces challenges such as limited workspace and human resources. Digitally supported HIV self-testing (HIVST) provided in clinics shifts testing to the client, potentially empowering the client, and addresses such constraints.

Objectives

The study primary objective was to determine the feasibility of integrating digitally supported HIVST into the clinic. Secondary objectives were to describe HIV testing volume, populations reached, and antiretroviral treatment (ART) initiation.

Method

We conducted an analysis of prospectively collected data during implementation of digitally supported HIVST in two healthcare facilities based in South Africa from June 2019 to September 2019. We described implementation and client characteristics using HIVST and compared testing before and during implementation.

Results

During the 4-month implementation period there were 35 248 client visits. A total of 6997 (19.9%) of these visits involved HIV testing. Of those testing, 2278 (32.5%) used HIVST. Of the 2267 analysed, 264 (11.6%) were positive: 182 (12%) women and 82 (11%) men. Of those, 230 (95.4%) were confirmed HIV positive and 150 (65%) initiated ART within 14 days. During a four-month pre-implementation period, 14.5% of the clients tested for HIV. Compared to the pre-implementation period, we observed a 25% increase in HIV testing.

Conclusion

Digitally supported HIVST increased the number of clients completing HIV testing in the health facility, without a need to significantly increase staff or space. Facility- based digitally assisted HIVST has the potential to increase HIV testing in high HIV prevalence clinic populations.

Background

HIV testing is the first step in linkage to HIV care, including prevention or treatment services [1,2]. The United Nations Joint Programme on HIV/AIDS has set interim 95-95-95 targets: that 95% of people living with HIV know their HIV status, 95% of these are to be initiated onto antiretroviral treatment (ART), and that 95% of these should be virally suppressed by the end of 2030 [3]. By the end of 2019, HIV testing services (HTS) had reached about 87% of people living with HIV (PLHIV) in the Eastern and Southern African region and up to 92% of the overall population in South Africa [4]. Of all HTS strategies, facility-based HTS is the mostly widely utilised, with 70% of all testing in South Africa occurring in public clinics and hospitals [5]. Individuals who test HIV positive during facility-based testing have higher subsequent engagement in care, presumably because they are already seeking clinical care and interacting with the medical system [6,7]. However, challenges such as limited space and limited human resources are major constraints to the daily test volume [8,9]. A second testing challenge is limited acceptability of standard HTS for some clinic clients [10,11,12]. Innovative strategies could increase testing volume and improve outreach to a greater proportion of clinic clients.

In 2015, the World Health Organization recommended the addition of HIV self-test (HIVST) as a complementary approach to standard HTS [13,14]. South Africa updated its HIV counselling and testing guidelines and adopted this recommendation [15]. HIV self-test is a process whereby a lay-person collects his or her own specimen (usually a buccal mucosa swab), performs the test, and interprets the result [16]. It is generally acceptable and is preferred by some clients, especially from hard-to-reach populations [17].

HIV self-test shifts testing to the client, potentially empowering the client, while also reducing human resource and space demands on the clinic. If conducted within a clinic, HIVST has the potential to substantially increase the overall HIV testing capacity of the facility. Considerations for HIVST centre around a client's ability to accurately collect the specimen, conduct the test, and interpret HIV results [18,19].

HIV self-test using OraQuick test kits has shown high acceptability due to its non-invasive and easy-to-perform nature; however, some clients express the need for assistance, which may not be possible when the test is conducted without a health worker present during testing [20,21]. In addition, post-test guidance may support the client's health journey, and confirmatory testing is needed for positive HIVST results as part of the HIV testing algorithm.

In prior work, we identified that < 10% of patients visiting the facility received HIV testing [9]. A major barrier to increasing testing was lack of space and testing personnel. In response to these challenges, we developed a digitally supported HIVST system for facility-based use. The digital

platform was designed to shift testing guidance from personnel and to provide standardised guidance and counselling content, thus overcoming the limited supply of HIV counsellors. Self-testing by clients in small kiosks maintained privacy while overcoming the challenge of limited space from counsellor-led testing. The digital support is a software application installed on a digital tablet that provides content on conducting HIVST, steps after testing, and living with HIV, as well as a countdown timer for the testing process. This software was co-created by Aviro and The Aurum Institute to define and assess a delivery model of digitally supported HIVST in a health-facility setting. The primary objective of this study was to determine the feasibility of integrating digitally supported HIVST into the clinic; secondary objectives were to describe HIV testing volume, populations reached, and ART initiation.

Methods

We collected data from February 2019 to May 2019 prior to implementing HIVST (baseline), and from June 2019 to September 2019 during pilot implementation of digitally supported HIVST (implementation), for a before-and-after comparison of HIV testing volume and HIVST use.

Setting

The study was conducted in the Ekurhuleni district located in the Gauteng province of South Africa, outside the city of Johannesburg. In 2019, the City of Ekurhuleni had a population of 3 774 638 and a land size of 1975 km^2. Ekurhuleni comprises urban and peri-urban residential areas with a total of 93 public health clinics and 6 public hospitals. All public health facilities provide HTS free of charge. This study was conducted in two public community healthcare facilities. Both facilities are in urban areas and each had an average daily headcount of 400 clients; each operated for 8 hours per day. Both facilities had primary care providers who were professional nurses, with a medical doctor visiting up to three days per week.

These facilities provide primary health services, including acute and chronic care, family planning, antenatal care and childhood immunisations. In both facilities, free HTS were provided by trained lay counsellors.

One facility had five, and the other six, lay counsellors. Both facilities allocated two rooms/workspaces for HTS inside the facility and two foldable gazebos outside the facility that provided additional private space for HTS delivery. These facilities were selected in coordination with the district-level Department of Health to pilot the digitally supported HIVST.

HIV testing services

Posters regarding HIV testing were prominently displayed in the clinics and health talks were conducted in waiting areas during baseline and implementation periods. During the

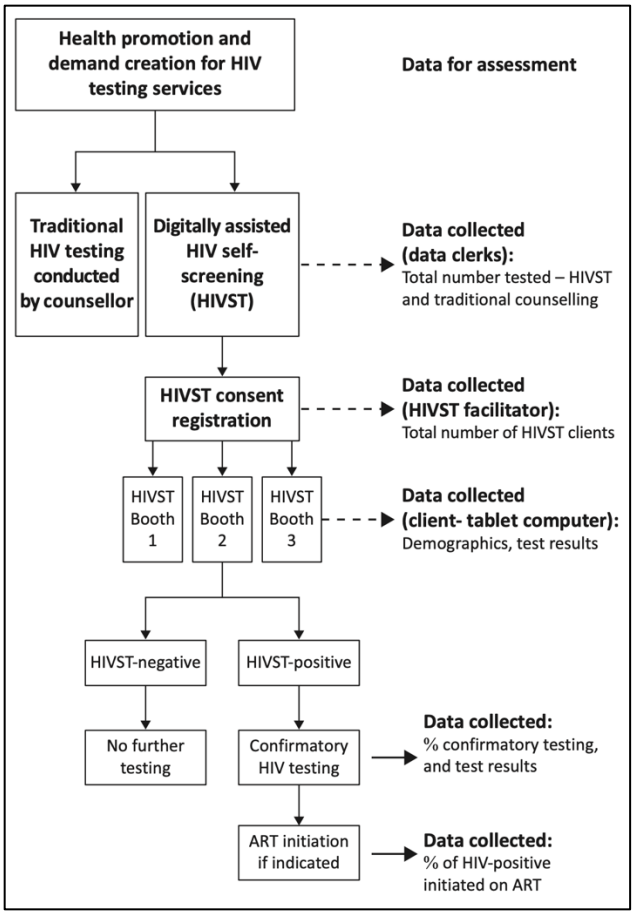
implementation period these talks informed clients about standard testing provided by counsellors and HIVST using OraQuick.

Standard HIV testing

When a client accepted standard HIV testing, they were sent to a counselling room or a gazebo where a counsellor would provide the service to one client at a time. Standard HTS takes a median of 26 min, as we have described from prior work in public clinics in this district [9].

HIV self-testing

OraQuick information brochures, translated into several local languages, were distributed to clients in waiting areas to give them more information about self-testing. Figure 1 shows the client flow from information to completion of confirmatory testing.



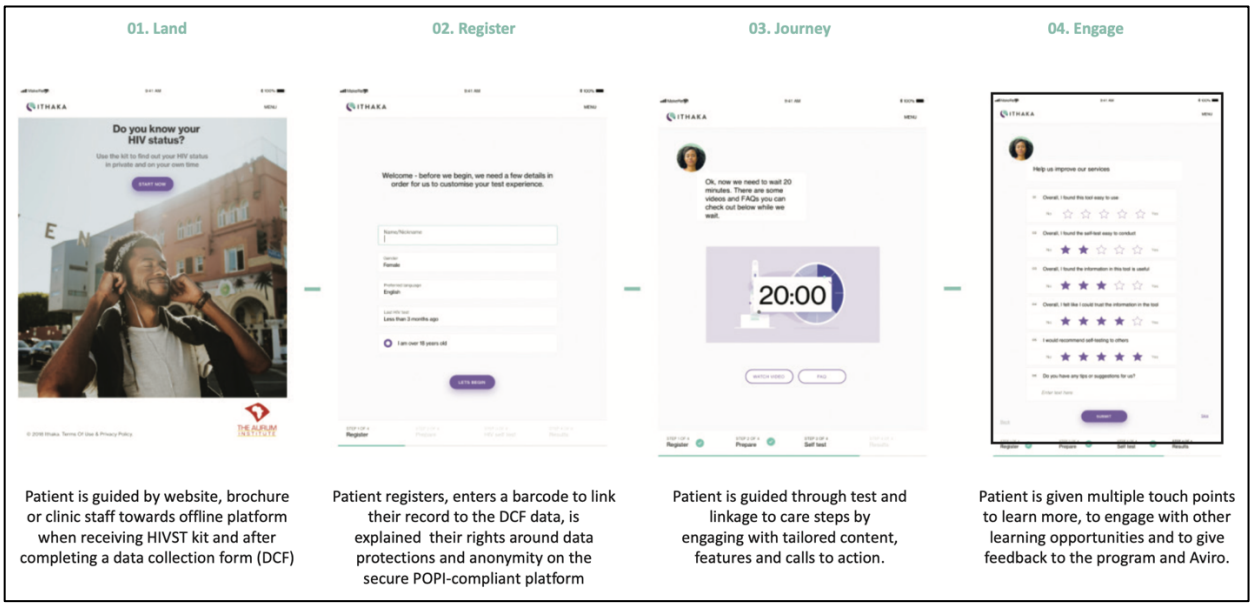
ART, antiretroviral treatment; HIVST, HIV self-screening.

FIGURE 1: Facility HIV testing flow incorporating digitally supported HIV self-test.

Three 1 m × 1 m HIVST booths were placed inside each health facility. Each booth had pictorial instructions to guide the testing process, an OraQuick® HIV Rapid Antibody Test (OraSure

Technologies, Inc., Pennsylvania, United States [US]), a tablet device with the digital application, and headphones for clients to listen to audio content on the digital application. OraQuick is a lateral flow test for antibodies using a specimen from an oral mucosal swab.

Each facility had a dedicated HIVST facilitator, trained in HIV testing and the digital platform and allocated to facilitate digitally supported HIVST. HIV self-test facilitators requested written consent for HIV testing, and a separate written consent to use the digital application, as it was implemented as a pilot study. HIV self-test facilitators also assisted clients when called upon. HIV self-testing was supported by a digital application delivered through a tablet device in each HIVST booth (Aviro Pocket Clinic, Aviro Health, Cape Town, South Africa) that provided audio-visual content via the screen and attached headphones. The digital support sought to guide a client's HIVST journey from testing to next steps after a negative or positive test. The journey started with the client agreeing to terms of use and data collection and registering demographic information (Figure 2).



POPI, Protection of Personal Information.

Figure 2: Digital support journey.

Clients were then guided through pre-test counselling, testing (including a video demonstrating the use of the OraQuick HIV test kit), and post-test counselling. The content features, voice, and examples were tailored to the client's age and sex as entered at the start of the session. After self-sample collection from the buccal mucosa, the client was prompted to set the on-screen timer. During the 20 min waiting period for the OraQuick results, the client was led through audio- visual health-related content regarding HIV and HIV testing. After the 20-min OraQuick development time was completed, the client was asked to enter the test result. Further audio-

visual post-test counselling was provided based on the entered test result. The client also had the option to get assistance from the HIVST facilitators.

Individuals who tested positive were reminded of the need for a confirmatory test as per the South African algorithm. If the client agreed, the facilitator escorted the client to a lay counsellor to conduct a confirmatory test. If they declined testing, the facilitator documented this. If both screening and confirmatory test results were positive, linkage to HIV care was initiated.

Data collection

Data were retrospectively abstracted from clinic paper testing registers to identify unique individuals, testing outcome (positive or negative), sex and age grouping.

HIV self-test facilitators, funded by the study, recorded sex, age, history of HIV testing, and HIV test results for all clients opting for HIVST. For those patients with a positive HIV test result with HIVST, we abstracted available ART data from the electronic record system and patient paper files (we did not assess linkage to ART for patients receiving routine HTS). Facility headcounts were tabulated daily by clinic staff using a register that listed all clinic clients.

Abstracted data were queried for missing information. Clinic source documents were reviewed to resolve queries and update the study database.

Analysis

We sought to describe operational and technical feasibility based on whether the HIVST kiosks could be used within the overall clinic flow and whether their use was sustained during the pilot period (e.g. without equipment breakdown), whether clinic clients would use the HIVST system, whether the digital tablet assistance was used by clients, and whether testing was completed with results. This was based primarily on the experience of the HIVST facilitators and supported by results of HIVST volume. Data were analysed using STATA© version 16 (2019, StataCorp LLC, College Station, Texas, US). We calculated the median age of the patients testing for and diagnosed with HIV before and during the implementation phase. Additionally, numbers and proportions were used to report categorical variables. We further calculated percentages of HIV confirmatory test outcomes and linkage to ART for the categories listed above. We also calculated percentages for HIV test volume and test outcome for the baseline and implementation periods. We used the chi-square test to compare the proportion of clients receiving HTS pre-implementation and while HIVST was being implemented.

Ethical considerations

An application for full ethical approval was made to the Witwatersrand Human Research Ethics Committee and ethics consent was received on 11 February 2021. The ethics approval number is 201111. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Additionally, as per HIV testing guidelines, all clinic attendees who participated in the Aviro Pocket Clinic HIVST provided consent to HIV testing and counselling. For this analysis, all data variables were de-identified.

Results

During the 4-month pre-implementation baseline period, there were 34 393 client visits, with a total of 4999 (14.5%) involving HTS. The majority of clients testing for HIV were women (n = 3474; 69.5%); 541 (10.8%) tested HIV positive. The median age of those testing positive was 34 years (interquartile range [IQR]: 28–40 years).

Table 1: Characteristics of patients who used the Aviro Pocket Clinic HIV self-test platform in the two pilot health facilities.

Variable	*n*	%
Gender		
Female	1535	67.70
Male	732	32.30
Age		
≤ 24	675	29.80
25–35	1090	48.10
36–49	412	18.20
≥ 50	82	3.60
Missing	8	0.35
HIV status		
Reactive	264	11.60
Non-reactive	2003	88.40

N = 2267

During the 4-month implementation period, there were 35 248 client visits in the two health facilities. A total of 6997 (19.9%) of these visits involved HIV testing. Of those testing, 2278 (32.6%) used HIVST. We excluded 11 patients from the analysis because they were below 18 years of age. Among the 2267 clients who used HIVST, 1535 (67.7%) were women (Table 1). The median age was 28 (IQR: 24–33 years). The median age of those testing positive was 33 years (IQR: 27–38 years). The majority of clients using HIVST were aged 18–35 years (Table 1).

HIV diagnosis

Of the 2267 clients that used HIVST, 1535 were women and 732 were men (Table 1). A total of 264 (11.6%) were positive on OraQuick, with a similar proportion of women (182/1535; 12%) and men (82/732; 11%) testing positive. One hundred and thirty-five/264 (51.1%) of those testing HIV positive were aged 25–35 years old; 18/264 (6.1%) were aged ≥ 50 years.

Of the 264 clients who screened HIV-positive, 241/264 (91.3%), received a documented HIV confirmatory test, of which 230/241 (95.4%) were confirmed to be HIV-positive. Of those who were confirmed HIV positive, 150/230 (65%) initiated ART at the same clinic within 14 days; overall, 184/230 (80%) initiated ART within nine months at the same clinic at which they had the testing.

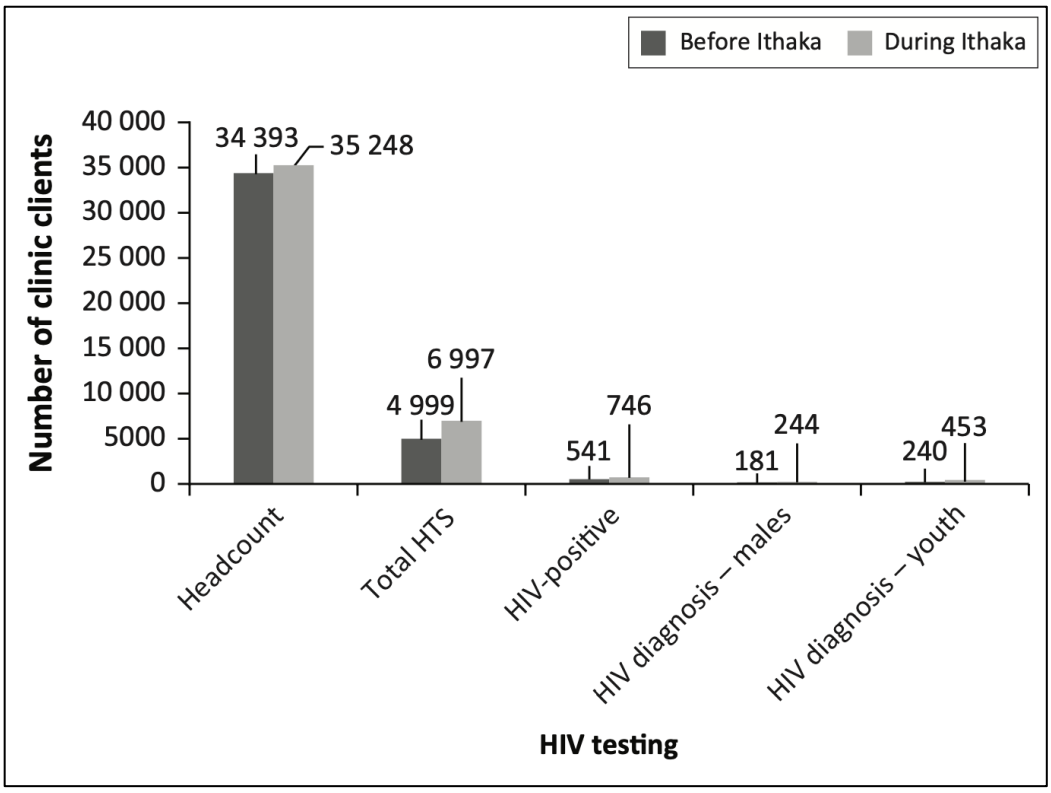


FIGURE 3: Comparison of facility HIV testing services before and during Ithaka (1 February 2019 – 30 September 2019).

Role of digitally supported HIV self-test in overall facility HIV testing services

The HIVST programme increased overall facility HIV tests of patients aged 15 years and above by 25% (14.5% vs 19.9% of clients testing; chi-square $P < 0.001$), while maintaining a stable HIV testing yield of 11% (Figure 3). The HIVST positivity yield was 12% – similar to traditional HTS. Importantly, the use of this platform almost doubled the number of youth (aged 18–35) diagnosed with HIV, increasing from 240 to 453 (Figure 3).

Discussion

Clinic-based digitally supported HIVST increased HIV test volume without decreasing the HIV testing yield in a pilot study in two clinics in South Africa. Clinic-based HIVST was able to increase volume without requiring increased space and with only a modest increase in human resources. HIV self-test has considerable promise that includes demonstrated acceptability [22,23] and access to more difficult-to- reach populations [24,25]. Our study builds on prior work of digitally supported HIVST that took place in patients' homes. Using this method, it was found that 70% patients logged into the digital application, and 22% reported their HIV test results. The acceptability of digital HIVST support has previously been reported from a qualitative study [26]. A meta-analysis of digital support for HIV testing noted that digital support increased HIVST when compared with its absence [27]. The acceptability and usability of the specific digital support platform used in this study (Aviro Pocket Clinic, previously named Ithaka [28]), as well as other digital platforms used in community or clinic testing, have previously been reported [26,27,28]. Prior studies of facility HIVST have reported an increase in HIV testing compared to standard HIV testing. A study of facility-based HIVST that did not use digital assistance required a considerable increase in healthcare worker resources and increased space to complete the testing [29,30].

Compared to HIVST conducted away from health services, health facility-based HIVST has the value of being able to rapidly provide confirmatory HIV testing and initiate ART among those testing positive.

Notably, studies of HIVST conducted away from health services often have limited data on HIV test outcome, confirmatory testing, and linkage to ART [22,31]. Facility-based HIVST has the additional value of being able to directly engage clients in prevention programmes, such as pre-exposure prophylaxis for those at high risk.

In South Africa and similar settings, space and personnel limitations are a major constraint on the capacity of routine HIV testing [9,32,33]. With digitally supported clinic-based HIVST, the client manages testing and content can be tailored to the client's age and gender. This shift from healthcare worker to client testing considerably reduced the human resource requirement, enabling one health worker to provide self-testing support to multiple individuals in private kiosks situated inside a clinic. It is plausible that empowering the client with testing may enhance subsequent care engagement. The digital support element allowed for a uniform content that promoted HIV prevention and the HIV care continuum engagement. We believe that this has the potential to overcome counselling quality and content challenges with current lay-counselor-provided post-test counselling [34].

The strength of this study is the integration and assessment of HIVST into routine care offered by regular service delivery personnel in public clinics, with minimal intrusion by study staff.

A limitation is that only two sites were studied for a relatively short period of 4 months and we relied on a comparison of pre-test data at the same sites over a similarly short period. In addition, we relied on routinely collected data (collected through routine health systems and the Aviro Pocket Clinic). This limited the range of available data and may have affected data quality. For example, we only had age data from the pre-implementation period for individuals who tested HIV positive and not all individuals accessing HTS. Finally, pre and post comparisons are subject to secular trends unrelated to the study intervention. We conducted the study over a short timeframe which limits the potential of this confounder, but does not eliminate it.

Conclusion

Use of technology to support the HIV care continuum from HIVST to ART initiation to retention in care has the potential to contribute to improved proportions reached along the HIV care continuum. Reaching updated 95-95-95 targets will require the use of novel and innovative care engagement approaches. Our data support the proposition that digitally supported HIVST platforms (and, potentially, other components of the care continuum) enable the shift of the care dynamic toward the client and client-centred care. Further studies of HIVST implementation and scale-up and digital support platform optimisation are needed to increase HIV testing and diagnosis to reach current targets.

Acknowledgements

Competing interests

Two authors, A.F. and L.S., are employed by the company that developed the digital support platform. All other authors declare that no competing interests exist.

Authors' contributions

The protocol was developed by C.J.H., T.M. and L.S.; data collection was by N.T.M.-P. and D.T.; data analysis was by N.T.M.-P. and C.J.H.; and the first draft manuscript was written by N.T.M.-P. All authors reviewed and revised the final manuscript.

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Data availability

The data sets used and analysed for this study are available from the corresponding author, N.T.M.-P., on reasonable request.

Disclaimer

The views expressed in this article are those of the authors and not an official position of the institutions or CDC (funder).

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Part 3. Consent and regulation as future considerations

CHAPTER 9. The evolution of HIV self-testing and the introduction of digital interventions to improve HIV self-testing

This chapter is based on:

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Author contributions: **Fischer AE:** Conceptualization, Methodology (lead), Writing- Original draft preparation, Visualization, Project administration. **Abrahams M:** Supervision (supporting). **Shankland L:** Resources. **Lalla-Edward ST:** Writing- Reviewing and Editing (supporting). **Edward VA:** Funding acquisition, Methodology (supporting). **De Wit J:** Supervision (lead), Writing- Reviewing and Editing (lead).

Abstract

HIV self-testing (HIVST) complements traditional HIV testing programmes by removing barriers and increasing access to testing for key populations, and digital interventions have been developed for HIVST to improve the testing and linkage to care experience for users. The first HIVST kit was proposed in 1986, but it took 10 years for the home sample collection (HSC) HIVST to become available and another 16 years for rapid diagnostic test HIVST to be approved by the Food and Drug Administration. Since then, studies have shown high usability and performance of HIVST, which led the World Health Organization formally recommending HIVST in 2016, and currently almost 100 countries have incorporated HIVST into their national testing strategy.

Despite the popularity, HIVST present challenges around pre-and post-test counselling, as well as the ability to report results and link users to care, and digital interventions for HIVST have been introduced to address these challenges. The first digital intervention for HIVST was introduced in 2014 and showed that digital interventions could be used to distribute HIVST kits, report results and link users to care. Since then, dozens of studies have been conducted, which have validated and expanded on these early findings, but many were pilot studies with small sample sizes and lacked the standardization of indicators required to aggregate data across platforms to prove impact at scale. For digital interventions for HIVST to be championed for scale-up, they must continue to show measurable impact at larger scales, while still maintaining and standardizing data security and integrity.

Introduction

Individuals can quickly learn their HIV status, independent of a healthcare facility, by collecting and testing their own specimen (blood drop from finger prick or an oral swab) with a variety of different HIV self-testing (HIVST) kits [1]. HIVST can improve traditional HIV counselling and testing programs by removing barriers associated with stigma and time to access traditional testing, while also promoting frequent testing which may lead to earlier diagnosis and treatment of HIV [2]. Although these benefits may be well known now [3], it took decades of research and policy shaping for HIVST to reach this state. In 1986, Elliott Millenson first proposed the idea of using home-based HIVST [4] and now, three and a half decades later, more than 10 million HIVST kits are being distributed each year [5].

Progress over the first 25 years was slow due to a lack of knowledge and policies for HIVST [4,6], however once the first rapid diagnostic test (RDT) HIVST kit became commercially available in 2012 [7], this allowed for research to be conducted into the usability and performance of HIVST, creating a strong body of evidence. This body of evidence now consists of 32 randomly controlled trials (RCTs) and over 150 values and preference studies, which shows high usability, acceptability and feasibility, in a variety of demographics and regions, while maintaining linkage to care rates, especially in key populations. These outcomes have led to the WHO formally recommending HIVST, and nearly 100 countries adopting them into their national HIV strategies [1,3].

HIVST has become an effective way to complement existing HIV testing strategies, especially for key populations, however they still present a few challenges for users and healthcare systems in general [1]. One main challenge is the lack of appropriate pre-test and post-test counselling [8], while another is that the usage of each self-test cannot be verified or tracked, so not all positive cases are appropriately linked to care [9,10]. To address these challenges, digital interventions for HIVST have been introduced in a variety of ways, including apps, websites and messaging platforms [11-13], and there is now a growing body of evidence that supports digital interventions for HIVST [14]. This descriptive perspective will present the evolution of HIVST, including the current challenges, then explore how digital interventions for HIVST are beginning to address these challenges.

The evolution of HIVST

Laboratory based HIV testing was first made available in 1985, and in many regions testing was introduced with legislation to protect people that tested positive from accidental disclosure and discrimination [15,16]. This legislation also introduced requirements for pre- and post- test counselling, consent to test and how HIV status could be reported, dictating how an HIV status was documented on medical records [4]. While these policies were developed to protect the tester and people living with HIV, requirements like reporting positives by name to confidential

registries and the need for face-to-face counselling inadvertently hampered innovative testing approaches like HIVST, as it could not comply with these obligations [15].

At that stage, there was inadequate information surrounding HIVST available to advise policy building, so understandably policies were shaped by the concerns of policy makers, surrounding the legal, ethical and social issues that could have potentially occurred from self-testing [17]. Legal concerns for HIVST included the inability for lay-people to correctly conduct the test, leading to false positives or false negatives that could spur litigation, while ethical and social concerns included psychological distress, and downstream effects, that may accompany a positive diagnosis outside a health facility. For example, in 1985, before life-saving ARV treatment, a man committed suicide in San Francisco after learning of his HIV positive status. During the first public hearing on HIVSTs, activists distributed copies of this person's obituary as a cautionary tale [4].

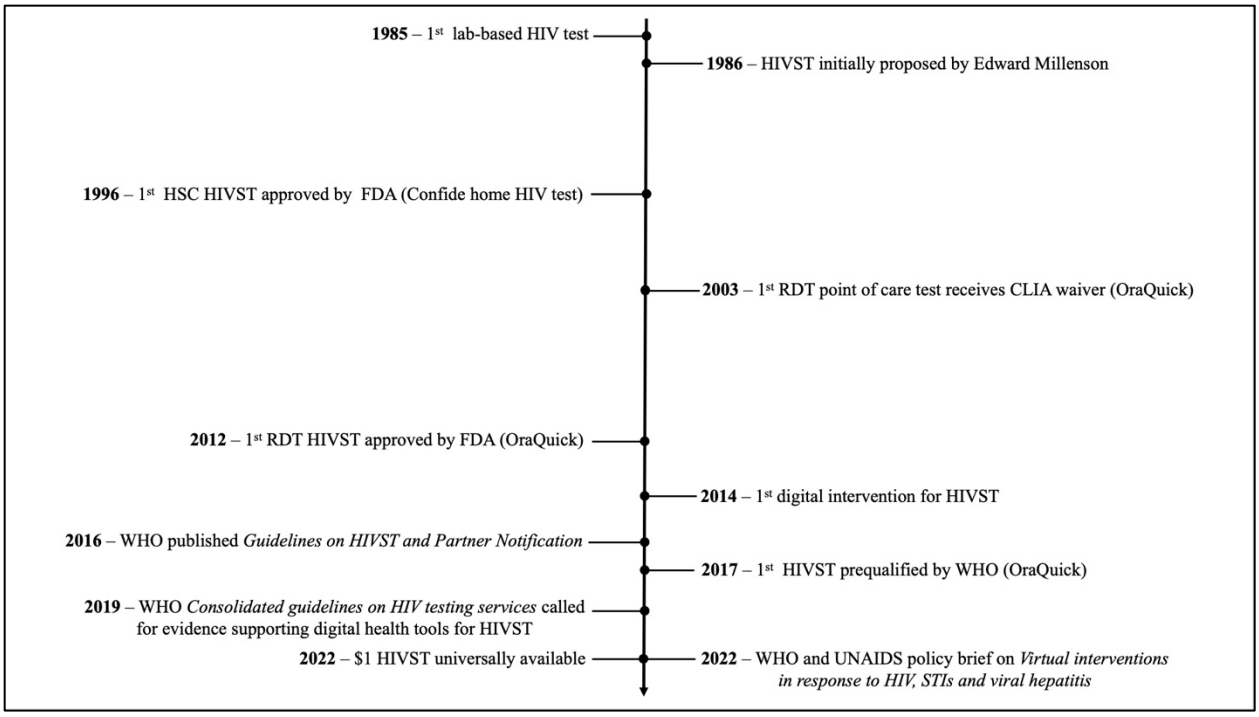

Figure 1. Timeline of HIVST and digital interventions for HIVST

FDA – Food and Drug Administration; HIV - human immunodeficiency virus; HIVST - HIV self-testing; HSC – home sample collection; STI – sexually transmitted infection; UNAIDS - The Joint United Nations Programme on HIV/AIDS; WHO – World Health Organisation

In 1996, with increasing availability of HIV treatment, the United States Food and Drug Administration (FDA) approved the first take-home HIVST kit, the Confide home HIV test by Direct Access Diagnostics (see Figure 1 for a complete timeline of HIVST evolution). Confide home HIV test was a home sample collection (HSC) test, which required a user to collect their own blood sample, mail it to a laboratory for analysis, then call a toll-free number a week or two later for

their results and the appropriate post-test counselling [16]. The HSC tests were marketed directly to end-users and during the first year of availability, almost 175,000 HSC tests were conducted, with no reports of suicide associated with the testing [16] Other studies have mentioned the possibility of social harm, but none have presented any evidence of suicide or harm related to self-testing [6,17,18].

Although HSC tests broke the home testing barrier, users still had to wait weeks before learning their result, and the HSC tests required blood samples from a finger prick, which proved difficult for some users [16]. To address these challenges, a new type of HIV test, the RDT, was developed, which could be conducted with an oral fluid specimen or blood, and the results were revealed in minutes, not weeks [19]. In 2003, OraQuick became the first RDT to be waived by the Clinical Laboratory Improvements Amendments Law, which was the first step towards becoming approved for HIVST. The OraQuick waiver did not allow for in-home testing like HSCs, but it did allow for point of care testing at doctors' offices, instead of just traditional laboratory settings [20].

RDTs proved to be easy to use and the short wait times meant that 30-40% of testers in public facilities were no longer being lost to follow-up before learning their results [19]. There were, however, concerns with accuracy, as the Centers for Disease Control and Prevention reported in a Morbidity and Mortality Weekly Report that one testing programme in New York City experienced clusters of false positives, which totaled over 400 from 2005-2008, exceeding the specificity confidence interval of the manufacturer [21]. The cause of these false positive clusters was not discovered, but it seemed to be an isolated incident, as no large-scale studies reported sensitivity (ability to detect true positives) or specificity (ability to filter out true negatives) values that fell outside the manufacturer's specifications.

The threat of inaccurate results may have delayed the HIVST approval process, but in 2012, the FDA approved OraQuick as the first ever over the counter RDT, joining HSCs as a faster option for HIV home testing [7]. Two years after OraQuick's FDA approval, a review of over 300 articles was conducted on self-testing, including 49 on HIVST, and the authors concluded that there was very little evidence of any harm (phycological, social or medical) because of HIVST. This review went on to recommend that HIVST programs should be expanded, and not restricted based on the potential fears of harm that self-testing may cause [17].

After the initial FDA approval, the development of HIVST programmes was slow, and as of July 2015, only two countries were implementing HIVST supported by national policies, but after the WHO released their Guidelines on HIV Self-Testing and Partner Notification in 2016 [1], there was a shift. Programmes like HIV Self-Test AfRica (STAR) were launched to study the use of HIVST in

low- and middle-income countries (LMICs), and their findings, as well as findings from other studies, began to show the true potential of HIVST [22]. A usability assessment with seven different HIVST products (Biosure, Atomo 1, Atomo 2, Calypte, OraQuick, Insti and Chembio), and almost 1500 untrained users was conducted in South Africa. The assessment reported that 96% of the participants thought the tests were easy to use and felt confident using them unassisted [23]. These findings were verified a year later by a study of four HIVST products (Biosure, OraQuick, Insti and Chembio), where 97% of the 3600 users, gave them high usability scores. Furthermore, this study revealed that the sensitivity and specificity of the tests was 98.2% and 99.8%, respectively, surpassing the performance measures attained during FDA approval [24]. This study was also conducted with a minimum sample size of 900 users per HIVST product, allowing the results to be used for WHO prequalification [25].

WHO prequalification is a programme that started in the 1980s as a way for UNICEF to determine whether the vaccines they purchased met appropriate quality standards [25,26]. Since then, the programme has expanded to include the prequalification of pharmaceuticals, including antiretrovirals (ARVs) and in vitro devices, including HIVST kits [27]. For HIVST kits, the prequalification process includes a review of packaging and instructions for use, evidence from studies on usability and clinical performance by untrained users, and a site visit of the manufacturing facilities [25]. In 2017, the WHO recognised OraQuick as the first prequalified HIVST kit, and now there are six HIVST kits that have WHO prequalification, including one that is available for only US$1 [5,28].

Despite the strong body of evidence leading to a formal recommendation by WHO, affordable WHO prequalified products, and supportive national policies in almost 100 countries, challenges with HIVST still remain [3]. HIVST can shift testing away from healthcare facilities, but this shift also removes the traditional pre-test and post-test counselling provided by trained healthcare workers or counsellors [8]. Furthermore, the shift away from facilities also creates a challenge around the ability to show that HIVST can create a measurable health impact, which is difficult because each individual self-test cannot be appropriately tracked and not all positive cases are linked to care [9,10]. Digital interventions for HIVST have been proposed to improve HIVST programmes by addressing these challenges and in 2019, the *Consolidated guidelines on HIV testing service*s was published by the WHO, which called for evidence supporting the potential for digital health tools to optimise HIVST. Specifically, the guidelines highlighted demand generation, video-based counselling and facilitating linkage to care as areas where evidence supporting digital interventions for HIVST is needed [29].

Digital interventions for HIVST

Digital interventions for HIVST are a type of digital health that incorporates digital technology, in the form of telehealth, apps, social media, messaging platforms or the internet, to complement HIVST by addressing the challenges of traditional HIVST programmes [30]. These digital interventions have been used to promote and distribute HIVST kits, deliver video counselling, provide instructions for use, and link self-testers to appropriate care, including preventative services, like preexposure prophylaxis, for negative self-testers and ARVs for positive self-testers [14]. The very first HSC programs for self-testing in the 1990s required users to call a toll-free number for their HIVST results, where they could also access pre-recorded information about their results, a textbook example of telehealth [31]. If that same telehealth programme was released today, it would be considered a digital intervention for HIVST, however this terminology did not exist in the 1990s, and the telephones and recordings may very well have still been analog, not digital.

To the authors' knowledge, the first digital intervention for HIVST that was academically evaluated, with findings published in a peer-reviewed journal was in 2014, within 2 years of the FDA approval of OraQuick. The intervention used a social networking app on smartphones, called Grindr, to increase HIVST by promoting a website that distributed free HIVST kits to men who have sex with men (MSM) in Los Angeles. In two months, nearly 12,000 people accessed the website, which led to 334 requests for HIVST kits, two of which tested positive and were linked to care [32]. This study showed potential for digital interventions to monitor public health impact by tracking positives and linkage to care. Since then, dozens of studies have been conducted to validate and expand on these early findings [11, 13, 14, 33, 34].

South Africa is one of the leading implementers of HIVST and building off the findings from the usability and performance assessments of HSTAR in sub-Saharan Africa [22-24], there was a series of compounding studies in the same region that illustrated the development of digital interventions for HIVST [11, 13, 33, 34]. The first study focused on the usability, acceptability and feasibility of digital interventions for HIVST, and findings confirmed that users found these digital tools highly usable and acceptable [11]. The study observed 300 South African users with no prior HIVST experience, while they conducted OraQuick self-tests, assisted by the Aspect smartphone app, a digital intervention designed to improve the testing and reporting experience for HIVST users. The *Aspect* app walked the user through the instructions for use, the collection and testing of their oral fluid specimen, then the reporting of results to a central database by uploading a picture of their self-test result. Of the 300 users, 296 (98.7%) found it easy to use, with 267 (89.0%) users correctly completing all steps and all but one (299/300; 99.7%) stating they would be willing to use the app again [11].

While the *Aspect* study was conducted under the supervision of a healthcare worker in a facility [11], another smartphone app, Ithaka was introduced, which let a similar sample of users from Johannesburg, South Africa self-test and report results at home, independent of a healthcare facility [13]. *Ithaka* was a progressive web app for OraQuick, which expanded from just instructions for use, by adding pre- and post- test counselling, before the user self-reported their results. The pilot included 751 users, which led to 295 (39.3%) receiving counselling and 168 (22.4%) self-reported results, including 14 (8.3%) that reported as HIV positive [13]. The *Ithaka* app was also adapted from the original home-based configuration, to complement facility-based HIVST as well. In the facility, visitors could self-test in a booth, guided by the Ithaka app, which provided digital instructions, followed by audio visual pre- and post- test counselling, as well as the ability to self-report results. The addition of digitally assisted HIVST with *Ithaka* led to a 25% increase in total testing numbers, without compromising the positivity yield [33].

Another South Africa study that paired OraQuick with a digital intervention for HIVST showed that digital interventions for HIVST could also successfully be used to link self-testers to care. Over 3000 participants from Cape Town were invited to do traditional HIV testing, supervised digital HIVST at the facility, or unsupervised digital HIVST off-site [34]. The digital intervention was *HIVSmart!*, an app that guided users through the instructions for use then linked patients to counselling and care; ARVs for positive self-testers and prevention pathways for negative self-testers. The conventional HIV testing (control) arm linked 98.5% of patients to care. The supervised digital HIVST arm was slightly lower with a 95.7% linkage to care rate and the unsupervised digital HIVST arm was slightly higher than the control with a linkage rate of 99.3% [34].

The above studies [11, 13, 33, 34] were presented for their similar methodologies and progressing outcomes, but these findings have also been validated by independent studies in different regions and populations [14]. A recent systematic review of digital interventions for HIVST confirmed that digital interventions could be used to link users to care, by aggregating findings from 12 studies, including studies from Asia, America and Europe. Five of the studies used social media or apps to link patients to care at a rate of 80-100%, which was more effective than the seven web-based platforms, where only 53-100% of users were linked to care [14].

This review also revealed one of the main challenges with digital interventions for HIVST, which is the lack of standardisation and cohesion across platforms. For example, linkage to care was not standard across all studies, and varied to include a clinic referral, post-test counselling, confirmatory testing, or ART initiation, depending on the study. This led the authors to suggest the need for a digital health framework focused on the diagnostic outcomes of HIV [14]. In 2022, at the International AIDS conference in Montreal, the WHO and UNAIDS released a policy brief

on *Virtual interventions in response to HIV, sexually transmitted infections and viral hepatitis*, which provides guidance for incorporating digital interventions into traditional programmes, including HIVST. This document champions the use of digital interventions for HIVST, while also attempting to standardise their implementation and indicators [35].

Conclusion

Despite challenges around counselling, reporting self-test results and linkage to care, HIVST has grown in use, especially over the past decade, with over 10 million HIVST kits currently distributed each year. Digital interventions for HIVST have been introduced in a variety of ways, and the research examining HIVST interventions chiefly consists of pilot studies that lacked ability to show impact at scale. This shotgun approach has also led to incompatible datasets across different interventions and regions, impeding data harmonisation and intervention scale-up. For digital interventions to realise universal acceptance, they must begin to show measurable, comparable impact at scale, while also maintaining data security and integrity. Future research needs to focus on large-scale implementation, and explore the need for regulatory approval or prequalification of digital interventions for HIVST, as a way to standardise these interventions beyond generic data privacy policies [36].

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CHAPTER 10. The readability of informed consent forms for research studies conducted in South Africa

This chapter is based on:

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Abstract

Background

Informed consent forms (ICFs) are used to obtain consent from participants. However the complexity and comprehensiveness of these forms may not be appropriate. Readability can be quantified by formulas in Microsoft (MS) Word, such as the Flesch Reading Ease test. The South African (SA) ethics guidelines suggest that the MS Word Flesch-Kincaid Reading Grade score should be used to assess the complexity of ICFs and should be the equivalent of grade 8 level, or lower.

Objectives

To use readability formulas to determine whether current SA ICFs are appropriate for the general population.

Methods

This was a descriptive study of a sample of English ICFs (solicited from our studies, as well as from local researchers) which received approval from local ethical review boards during the past 5 years, for prospective (≥6 months) drug studies that explored treatment and prevention of HIV, tuberculosis, diabetes or cardiovascular disease. ICFs were evaluated in MS Word for Flesch Reading Ease and Flesch-Kincaid Reading Grade, with the Simple Measure of Gobbledygook (SMOG) index calculated using www.readabilityformulas.com. Recommended targets for easy readability are above 60 for the Flesch Reading Ease score, and less than or equal to a grade 8 reading level for the Flesch-Kincaid Reading Grade and SMOG.

Results

A total of 75 consent forms from 35 individual research studies conducted in SA over the last 5 years were included. The consent forms had been approved by six ethics committees across seven of the SA provinces. The median (interquartile range (IQR)) Flesch Reading Ease score was 55.8 (48.7 - 59.7) and 18 (25.0%) of the ICFs had easy or standard readability, while the median (IQR) Flesch-Kincaid Grade was 10.2 (8.8 - 11.4), with 23 (30.6%) at least a grade 8 level or lower. The median (IQR) SMOG index was 9.8 (9.0 - 11.1) and 4 (5.3%) scored below grade 8 level.

Conclusions

Two-thirds of the ICFs from this study fail to meet the SA readability standard, a result matched by using alternative readability formulas. Readability can be improved with simple techniques and by actively monitoring readability metrics.

Background

Voluntary informed consent is an ethical and legal requirement for participation in clinical research studies, and informed consent forms (ICFs) are required to share information with participants who may come from a wide variety of backgrounds. These ICFs must effectively communicate information including participant rights, potential risks and benefits, complex medical information, and comprehensive study procedures. The complexity of these ICFs is compounded by additional requirements from legal departments and funders to ensure that internal policies and requirements are met. [1,2] Collectively, these components may lead to the creation of ICFs that certain populations may find difficult to comprehend.

The purpose of the ICF is to ensure that the potential research participant is given the essential information in a manner which is easy to comprehend so that their decision is a truly informed one.[3] Aside from the ethical aspects, the value of ensuring proper understanding by a potential participant is the increased likelihood of their compliance with study procedures and retention in the study.[4] However, a study on the understanding of ICFs among low-income participants in the USA found that only 45% of participants read the entire consent form, and 27% admitted that they only understood the study 'a little'.[5] Additional studies among different populations found that lengthy ICFs with medical jargon and complex concepts may take over an hour to fully read and comprehend.[1,6] An accepted metric of evaluation for these ICFs, and other medical information documents, is readability, which can be quantified using a number of tests, such as the Flesch Reading Ease test.[5] These readability tests have been globally applied to medical information documents and have constantly identified documents, including ICFs, that far exceeded local literacy levels.[8-10]

In South Africa (SA), informed consent has guidance from the Constitution of SA,[11] and the National Health Act 61 of 2003,[12] as well as international documents like the Declaration of Helsinki.[13] This has led to the creation of national guidelines to advise informed consent, which include Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa,[14] Guidelines for Good Practice in Health Care Professions: Seeking Patients' Informed Consent[15] and Ethics in Health Research: Principles, Structures and Processes.[16] Previous research has shown that these country- specific documents may not legally and ethically fulfil the complete requirements for informed consent;[17] however, in SA, universities have human research ethics committees (HRECs) that provide another level of guidance. HRECs may provide researchers with specific guidelines and templates for ICFs as part of the management of the entire ethics approval process.[18-20]

The adult literacy rate in SA increased from 91.9% in 2009 to 94.3% in 2017, while functional literacy (the ability to read at a grade 7 level) increased from 72.7% in 2002 to 86.3% in 2017, but

despite the increases in literacy rates, there is still a significant proportion of the population who struggle with these forms. When adults with a level of education lower than grade 7 were asked about filling out forms, 24% stated that they had difficulties doing so, while 36% were unable to fill out the forms at all.[21] Ethics in Health Research: Principles, Structures and Processes[16] is the only national document that directly speaks to readability, and states that readability levels should be appropriate to the participants' level of understanding, and suggests a complexity level of no more than grade 8. No readability studies have been conducted on the ICFs in SA. The objective of this study was to analyse the readability of ICFs used to obtain voluntary consent in SA research studies to determine whether the ICFs, as written, are appropriate for the general population.

Methods

Study design

This was a descriptive study in which parametric and non-parametric measures of central tendency and variability were used to describe the various algorithms used to evaluate ICFs. ICFs were included if they were English, had been approved by an SA HREC in the past 5 years, and were investigator-led prospective medium- to long-term (≥6 months) drug studies that explored treatment and prevention of HIV, tuberculosis (TB), diabetes or cardiovascular disease.

Recruitment

Participating ICFs were mined from a variety of sources from May 2019 until August 2019. A search of PubMed and Google Scholar was done to identify studies that met the abovementioned criteria; then the corresponding authors were invited via email to participate, by sharing their ICFs. Research and academic institutions were also contacted to invite researchers to participate. The email invitation included a line encouraging the researcher to forward this request to participate to their colleagues who may have also conducted eligible studies (email included in supplementary information).

Data collection

Consenting researchers were asked to provide a Microsoft (MS) Word document of their ICF for analysis. Where only PDF versions were available, it was exported as an MS Word document, then manually checked to ensure that all punctuation and formatting remained correct.

Readability metrics

The Flesch Reading Ease test incorporates average sentence length and average word length in syllables into a formula to compute reading ease, where the higher scores are easiest to read.[20] Scores from 70 to 100 are considered easy to read (appropriate for 4th to 6th grade), while scores from 60 to 70 are considered standard (7th or 8th grade) and scores below 60 are considered

hard (high school or college). A variation of the Flesch Reading Ease test is the Flesch- Kincaid Reading Grade, which uses the same variables, but weights them differently in order to provide a reading grade that directly parallels US school grades. Although developed for the American population, the Flesch Reading Ease test is one of the most accurate readability measures. It is commonly used globally and appropriate for our study.[1,9,10] Similarly, the Simple Measure of Gobbledygook (SMOG) index also provides a score that parallels years of education and has been proven highly effective for healthcare applications, including ICFs (Fig.1).[23,24]

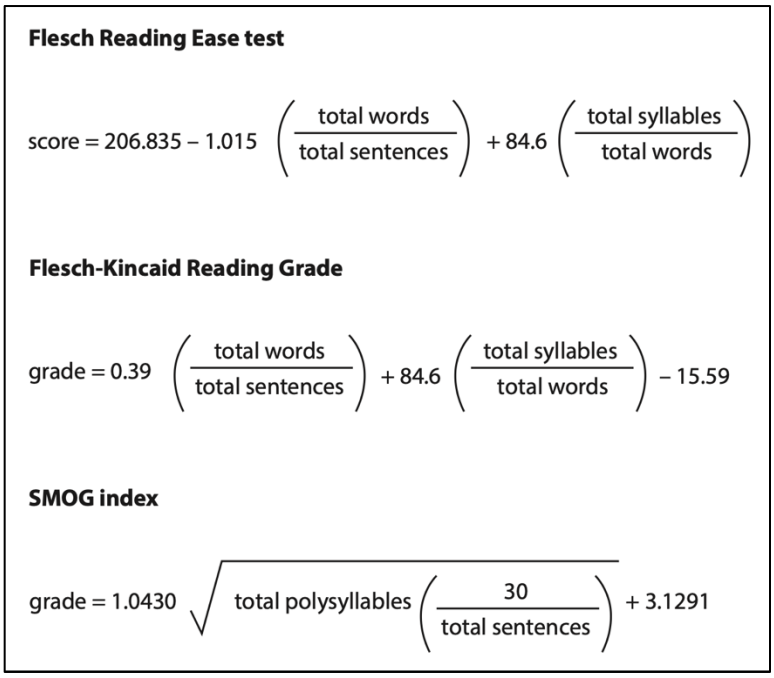

Figure 1. Readability formulas [10]
SMOG – Simple Measure of Gobbledygook.

Data extraction

A pre-defined data collection tool was created for data extraction of descriptive ICF characteristics (ICF type, HREC, study location, study type, disease of study, sample size, date, font type, font size and page length), variables associated with readability (word count, sentence count, sentence length, word length, total syllables, syllables per word and number of words with three or more syllables) and readability metrics (Flesch Reading Ease test, Flesch-Kincaid Reading Grade and SMOG index). Most ICF characteristics were collected by reading the documents, while readability variables and readability metrics were recorded from the MS Word 'Tools' toolbar, the online resource for readability metrics (www.readabilityformulas.com) (total syllables, word >3 syllables and SMOG index) or calculated (syllables per word and percentage of words with ≥3 syllables) from these collected variables.

In some instances, the word count in MS Word was not the same as the word count from the online resource because of certain formulas grading formatted symbols like bullet points or underlined areas for signatures differently. In these instances, the MS Word word count was taken as true. The online readability resource could only process documents up to 3 000 words, so large documents were processed as 3 000-word sections, then proportionally averaged back together based on the weights of each section. Syllables per word and words with 3 or more syllables were extracted from the online resource, but their respective average or percentage were calculated against the true MS Word word count, as the online calculator did not give results accurate to one decimal, and they were calculated with the internal word counter.

Data analysis

Extracted data were entered into MS Excel (Microsoft Corp., USA) for analysis. Data from ICF characteristic variables were counted, and then presented as frequencies and percentages. Median and interquartile ranges (IQRs) were calculated for all readability variables and the readability test scores. Means were not calculated to avoid presenting results skewed by a 20-page ICF. For each readability test, the scores were categorised as easy, medium and hard, and each of these categories was presented as a frequency and percentage.

Patient and public involvement

A member of a local institutional review board read and commented on the manuscript for tone and messaging. Aside from this, no patients or public were involved in the study design, or in the recruitment to, and conduct of, the study.

Results

ICF characteristics

There was a total of 75 ICFs, from 35 individual studies, with many of them including secondary consent forms. The most common secondary consent form was for bio-storage (9; 12.2%), followed by under-18 assent (5; 6.8%), parental consent (4; 5.4%), sub-studies (4; 5.4%), sampling (3; 4.1%), pregnant participants (2; 2.7%) and a variety of others. The consent forms were from six ethics committees across SA, with University of the Witwatersrand and University of Cape Town being the highest, with 22 (62.9%) and 6 (17.1%), respectively. Seven provinces were represented, with 20 (57.1%) from Gauteng Province and 7 (20.0%) from Western Cape Province being the highest. General research studies were the most prevalent type of study, with 13 (37.1%), followed by randomised controlled studies (9; 25.7%). Twenty-two studies (62.9%) focused on HIV, 7 (20.0%) on TB, 7 (20.0%) on non-communicable diseases and 6 (17.1%) on maternal health. The remainder focused on other health areas. Eleven studies (31.4%) had a sample size of 101 - 500, while 8 (22.9%) were below 100 and 6 (17.1%) were above 500; 10 (28.6%) did not provide sample size. The most common fonts were Calibri and Arial, 15 (42.9%)

and 12 (34.3%), respectively, while the most common font sizes were 11 and 12, both appearing 15 (42.9%) times.

ICF readability variables

The median (IQR) ICF length was 5 pages (4 - 7), 1 608 words (1 121 - 2 298), and 69 sentences (48 - 100). For sentence length, median (IQR) values were 19 words per sentence (17 - 20), and for word length, 4.7 characters/word (4.5 - 4.8). The median (IQR) ICF total number of syllables was 2 620 (1 739 - 3 653), with a median of 1.6 syllables/word (1.5 - 1.6). The median (IQR) number of words with 3 or more syllables was 248 (163 - 325), with a median percentage for the total words of 14.3% (13.3 - 16.8%) (Table 1).

Table 1. Readability statistics

	Average	Minimum	Maximum
Readability variables			
Page length	6.0	1.0	20.0
Word Count	2,182.2	310.0	9,418.0
Sentences	92.7	9.0	363.0
Words per sentence	18.5	13.1	25.4
Characters per word	4.7	3.8	5.1
Total syllables	3,402.5	558.0	14,498.0
Syllables per word	1.6	1.4	1.8
Words >=3 syllables	312.8	58.0	1,283.0
Words >=3 syllables(%)	14.8	8.0	23.5
Readability metrics			
Flesch Reading Ease	54.9	40.8	81.0
Flesch-Kincaid Reading Grade	10.1	6.9	13.5
SMOG Index	10.0	7.1	12.6

SMOG- Simple Measure of Gobbledygook

ICF readability metrics

The Flesch Reading Ease scores identified that the median (IQR) score was 55.8 (48.7 - 59.7), while 1 (1.3%) of the 75 ICFs had easy readability and 17 (22.7%) had standard readability. The median (IQR) Flesch-Kincaid Grade level was 10.2 (8.8 - 11.4), with 23 (30.6%) at a grade 8 level or lower. The median (IQR) SMOG index was 9.8 (9.0 - 11.1), while only 4 (5.3%) were at or below a grade 8 level (Tables 1 and 2).

Table 2. Readability scores

	Frequency	Percent
Flesch Reading Ease		
Scores from 70-100 (Easy)	1	1.3
Scores from 60-70 (Standard)	17	22.7
Scores from 0-60 (Hard)	57	76.0
Total	75	100.0
Flesch-Kincaid Reading Grade		
Grade 0-6 (Easy)	1	1.3
Grade 7-8 (Standard)	22	29.3
Grade 9-college (Hard)	52	69.3
Total	75	100.0
SMOG Index (online)		
Index 0-6 (Easy)	0	0
Index 7-8 (Standard)	4	5.3
Index 9 and above (Hard)	71	94.7
Total	75	100.0

SMOG- Simple Measure of Gobbledygook

Discussion

This study has determined that over two-thirds of the ICFs analysed were hard to read and required an average reading comprehension level equivalent to at least a US grade 10. This exceeds the national functional literacy level of grade 7,[21] as well as the recommended grade 8 level as outlined in Ethics in Health Research.[16] These findings are in line with similar studies from different regions, such as a 2017 study in the UK that identified the Flesch Reading Ease score of a standardised orthopaedic procedure consent form to be 55.6, which may impede a significant percentage of patients from providing informed consent.[2] Another study revealed that patient information leaflets in the UK required graduate level reading ability, which is too high for most HIV-positive individuals to effectively provide informed consent.[10]

Despite these readability and literacy disparities, research studies continue to enrol study participants, which raises the concern of whether participants' consent is sufficiently informed. Concerns about participant understanding of ICFs, independent of readability considerations, have been documented since as early as 1981.[25] Since then, there is very little evidence to show that efforts have been made to improve the understanding of ICFs; instead, they are actually increasing in complexity.[26,27] In 2005 the HIV Prevention and Trials Network proposed a framework for enhancing informed consent, highlighting the importance of writing at no more than a grade 8 reading level; however, in the sub-Saharan African context, comprehension can be further compromised by low literacy rates, and vocabulary and translation difficulties.[28]
For research studies that target the general population in SA, providing consent may prove challenging for all individuals that read below the grade 10 level, including the 14% of the population who are not functionally literate (below grade 7). This challenge is exacerbated in

ageing populations who are increasingly required to participate in non-communicable disease research.[21] In order to remove this readability barrier from ICFs, the Flesch-Kincaid Reading Grade and SMOG index should target grade 8 or less for the general SA population, while the Flesch Reading Ease test should target scores above 70 for the general population. This is evident as general interest magazines and tabloids have Flesch Reading Ease scores of 80 and 95, respectively, while intellectual newspapers like The New York Times and The Wall Street Journal have scores in the 40s.[10]

The two main variables that impact readability are the number of words per sentence and the number of syllables per word, with long sentences and words containing three or more syllables resulting in poor readability scores.[10] By utilising the free and accessible readability tests online and in MS Word, researchers are able to evaluate and modify the readability of their ICFs to ensure that they are appropriate for their target population. This could remove barriers to entry for participants with lower reading comprehension levels, creating a more complete sample, while also ensuring that participants are aware of the potential benefits and risks of participation. Additional resources available to assist researchers in reaching their readability goals include the Program for Readability in Science and Medicine (PRISM) Readability Toolkit, which guides researchers through the principles of readability, how to determine readability, a quick-guide to improving readability (including an editing checklist), samples of easily readable ICF excerpts and examples of plain language replacements for complex medical jargon.[7] Equipped with this knowledge, researchers should be able to improve readability by keeping sentences short (below 15 words) and by ensuring that their ICFs consist of mostly one- and two-syllable words.

Study strengths and limitations

To our knowledge this is the first report of ICF readability in sub-Saharan Africa. The method of recruitment may have led to a sampling bias, as researchers may have declined to participate based on the complexity of their ICFs, underestimating readability. Network- and consortium-managed studies had strict access and sharing policies, which decreased the number of ICFs and studies that could be included. The readability formulas did not take into account other factors that may affect readability such as font, paragraph spacing and content.

Conclusions

The SA publication Ethics in Health Research[16] clearly outlines that the Flesch-Kincaid Reading Grade tool should be used to assess the complexity of ICFs and that the targeted complexity should be no more than a grade 8 level equivalent. Two-thirds of the ICFs included in this study exceed these recommendations. However by monitoring readability metrics and employing simple techniques to increase readability, national targets could be met. Furthermore, these targets could be monitored by HRECs to ensure that these readability barriers are decreased.

Declaration

The University of the Witwatersrand Human Research Ethics Committee approved this evaluation (ref. no. H19/03/05).

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Author contributions

Designed the study: AEF, WDFV, SC, STL-E. Analysed the data and interpreted results: AEF, STL-E. Wrote the initial draft: AEF, STL-E. All authors critically reviewed and approved of the final draft.

Funding

None.

Conflicts of interest

Some of the included ICFs were from studies in which AEF, WDFV and STL-E were part of the study team. All authors have no further competing interests to declare.

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Supplementary Information. Recruitment email

Dear [name of researcher]

My name is Alex Fischer and I am a researcher at the University of Witwatersrand Reproductive Health & HIV Institute (Wits RHI) in Johannesburg. I am currently undertaking a research project, and I am investigating **The Readability of Informed Consent Documents for Research Studies Conducted in Johannesburg, South Africa.** The aim of this research study is to establish whether informed consent forms (ICFs) used in South African medical research studies are easy to read and if the text is easy to comprehend.

As part of this research study, I came across "[title of research project]" I would like to invite you to take part by sharing with us any informed consent documents from this study, and any other medical research studies that you have worked on over the last five years. We ask that you provide a Word Document of your ICD that we can analyze for readability while maintaining complete anonymity and confidentiality of the results.

If you are willing to participate, please sing and return the attached consent form. Please let me know if you have any questions or concerns, and I would be happy to address them.

Thank you,

Alex
+27 073 776 2705
afischer@wrhi.ac.za

CHAPTER 11. Should digital interventions for HIV self-testing be regulated with WHO prequalification?

This chapter is based on:
Fischer AE, Lalla-Edward ST, Edward VA, Abrahams M, Shankland L and De Wit J. Should digital interventions for HIV self-testing be regulated with WHO prequalification? WHO Bulletin (accepted for review 16 April, 2023)

Author contributions: **Fischer AE:** Conceptualization (lead), Methodology (lead), Writing- Original draft preparation. **Lalla-Edward ST:** Conceptualization (supporting), Writing- Reviewing and Editing (equal). **Edward VA:** Resources, Supervision (supporting). **Abrahams M:** Supervision (supporting). **Shankland L:** Project administration. **De Wit J:** Supervision (lead), Methodology (supporting), Writing- Reviewing and Editing (supporting).

Abstract

HIV self-testing (HIVST) allows people to test for HIV outside traditional health facilities, but this presents challenges around pre-and-post-test counselling, reporting results and linking to care. Digital interventions for HIVST, a type of software as a medical device (SaMD), have been shown to address these challenges, but there is currently no standardised system for regulating or approving these interventions. The WHO Prequalification Program (WHOPQ) is an international regulatory body that approves vaccines, medications, and in vitro diagnostics (IVDs), for low-and middle-income countries (LMICs) that do not have the capacity to do their own approvals. This article explores whether WHOPQ could be used to prequalify digital interventions for HIVST.

Over half the WHO member states have national regulatory bodies for medical devices, but LMICs, especially in Africa, do not have the capacity to regulate medical devices, let alone SaMD. This gap parallels the gap in vaccine regulation that initially led to the development of WHOPQ, and while sophisticated AI/ML-enabled SaMD are being developed, digital interventions for HIVST could be used as a low-risk test case for prequalification of SaMD. The WHOPQ already has a strong history with HIV; over half the WHOPQ funding is from HIV-related donors and half of all prequalified medicines and IVDs are for treatment and diagnosis of HIV, however, only 2% are manufactured in Africa. If WHO opts to enable prequalification of digital interventions for HIVST, they must consider accessibility for digital health companies from Africa and ensure that prequalification does not delay access to people testing for HIV.

Introduction

HIV self-testing (HIVST) allows an individual to conveniently learn their HIV status, by collecting and testing their own specimen (oral swab or blood drop from a finger prick) in the privacy of their own home [1]. In 2012, the first HIVST became commercially available when the Food and Drug Administration (FDA) approved OraQuick for over-the-counter sales in the United States [2]. Since then, a growing body of evidence has supported using HIVST to complement traditional HIV testing programmes toward achieving the UNAIDS 95-95-95 goals by 2030 [3]. In 2015, only two countries integrated HIVST into their national HIV strategy, but after the WHO recommended HIVST in the 2016 Guidelines on HIV Self-Testing and Partner Notification [1], then officially prequalified OraQuick in 2017 [4], the number jumped to over 40 [5]. Five years later, there are almost 100 countries that endorse HIVST in their national HIV strategy, as well as six prequalified HIVST kits, including one for just US$1 [6,7].

As HIVST gained global popularity, the shift away from healthcare facilities was recognized to present some challenges for counselling, reporting results and linkage to care [8,9]. In response, digital interventions for HIVST have emerged as a novel approach for closing these gaps [10-13]. Like other digital health platforms, digital interventions for HIVST use digital technology (apps, social media, messaging platforms or the Internet) to assist people through an HIVST journey [14]. These digital interventions have been used for demand generation to promote and distribute HIVSTs, but they are also being used to address the challenges experienced with HIVST. Evidence shows that digital interventions for HIVST can deliver standardised counselling, allow users to report results and link them to appropriate [13].

Before the COVID-19 pandemic accelerated the familiarisation of digital health [15,16], the WHO was already drafting its *Global Strategy on Digital Health 2020-2025* [14]. Subsequently, in 2022, UNAIDs and WHO published a policy brief on *Virtual interventions in response to HIV, sexually transmitted infections and viral hepatitis* [17]. These documents reaffirm a strong commitment to digital health interventions, including for HIVST, and introduce guiding principles and implementation frameworks. However, these documents do not outline a plan for regulating or prequalifying digital health interventions, unlike for HIVST kits [4]. This policy and practice article provides background on the WHO prequalification process and discusses reasons for, and challenges related to the WHO prequalification of digital interventions for HIVST.

WHO Prequalification

The WHO Prequalification Program (WHOPQ) is an international regulatory body that oversees the quality and safety of various medications and medical devices. While many high-income countries have their own regulatory bodies, like the FDA in the United States or the Medicines and Healthcare products Regulatory Agency in the United Kingdom [18], LMICs do not have the

capacity to ensure the quality of these goods, so the WHOPQ was established to serve these countries by identifying products that the WHO deems fit [19]. There are currently over 1,700 products on the WHOPQ list across four streams: vaccines, medicines, *in vitro* diagnostics (IVDs) and vector control [20].

The WHOPQ was launched in 1987 to standardise and scale the WHO's Expanded Programme on Immunization (EPI), which had been used since 1974 to determine whether the vaccines for tuberculosis (TB) (BCG) and Yellow Fever purchased by UNICEF met suitable quality, safety and efficacy standards [19,21]. In 2001, the medicines stream was introduced in response to the need for affordable, quality generic medications for the treatment of HIV/AIDS, which allowed the WHO to begin prequalifying generic antiretroviral drugs (ARVs). Most of the generic ARVs were produced in India, and many procurement agencies did not have confidence in the oversights provided by the Indian drug regulatory authorities, as there were no originator equivalents from highly regulated countries to compare them to [22].

Over the next decade, the prequalification program expanded to include generic medications for TB and malaria, followed by generics from the essential medicines list for reproductive health, pandemic influenza variants and diarrhea. In 2013, the medicines stream extended from finished pharmaceutical products to include the prequalification of the active pharmaceutical ingredients used to make medications [23]. The IVD stream was introduced in 2011 for the prequalification of HIV tests and expanded in 2013 to include male circumcision devices. In 2014, the IVD stream was re-designed to include tests for malaria, cholera, viral hepatitis and syphilis. Subsequently, in 2016, HIVSTs were added to the IVD stream. The vector control stream was also added in 2016 [23].

For a product to become WHO prequalified it must go through various assessments. The process varies somewhat across streams, but always starts with an invitation for expressions of interest for a specific product category released by the WHO. Manufacturers are invited to submit a cover letter, product dossier and product samples (including final packaging and instructions for use) to undergo evaluation against internationally accepted regulatory standards for safety, quality and efficacy [19]. The evaluation also includes a pre-submission screening for eligibility and inspections of the manufacturing and clinical trial sites, where applicable. If successful, the entire WHOPQ process can take up to one and a half years [24], costing the manufacturer up to US$31,000 in fees, depending on the product stream [25].

Reasons for prequalification of digital interventions for HIVST

Trends in digital health

Nearly 60% of the WHO member states have national regulatory bodies that regulate medical devices, and many of these countries have started to regulate and approve digital health interventions as a category called *Software as a Medical Device (SaMD)* [26]. A digital health intervention is considered an SaMD if it provides recommendations for the prevention, diagnosis or treatment of a disease to healthcare workers, patients or caregivers [18]. Most LMICs do not have the capacity to regulate SaMD, as they are still trying to develop regulatory processes for traditional medical devices. Of the 15 countries represented in the College of Surgeons of East, Central, and Southern Africa, seven have no regulatory processes, seven are currently in development, and only one, South Africa, has an established regulatory process for medical devices [26]. However, despite the established procedure, SaMD in South Africa do not yet require approval, although digital health interventions are considered a Class C IVD medical device, and the South African Health Products Regulatory Authority (SAHPRA) has committed to regulating all medical devices in the future [27].

The gap in regulatory processes for SaMD between high- and low-income countries [26] parallels the gap in regulation surrounding vaccines and medications that initially led to the development of the WHOPQ [19]. Since 2017, there have been no new streams added to WHOPQ. However, it has been suggested that the WHOPQ process could be expanded to include digital health technologies in the future [28]. This suggestion corresponds with the proposed actions of the WHO Global strategy on digital health 2020-2025, which includes the development of a WHO framework for assessing and regulating digital health technologies [14].

WHOPQ and HIV

The SaMD space is large and diverse, with an estimated 350,000 digital health apps ranging from simple educational chatbots to advanced AI algorithms that use machine learning for early cancer diagnoses [29]. There are approximately 50 peer-reviewed digital interventions for HIVST [13] that do not provide a diagnosis but are intended as a screening tool to educate users and link them to care for confirmatory testing and appropriate treatment [10]. Due to their small number and built-in screening-confirmation control, digital interventions for HIVST could provide a low-risk test case for the WHOPQ to develop preliminary prequalification guidelines for SaMD.

The WHO PQ also has a strong history in the domain of HIV. Although the programme started with the prequalification of vaccines, expansion into new product streams has been guided by the need to diagnose and treat HIV [23]. In 2002, the first medicine prequalified by the programme was Ritonavir, an ARV, and the ten other medications prequalified in the first year of the WHOPQ were all for treating HIV. A decade later, when the prequalification of IVDs was

added to the programme, the first prequalified IVD was for malaria, then the following six were all for the diagnosis of HIV. Currently, almost half the prequalified medicines (46%; 297/646) are for the treatment of HIV and more than half of the IVDs (57%; 62/109) are for HIV diagnosis [4].

Since 2006, the primary WHOPQ donor has been UNITAID, whose mission is to increase access to treatment for HIV, TB and malaria, especially in LMICs. In 2017, UNITAID accounted for over half the WHOPQ budget, with supplementary funding from other HIV-related donors, including the Bill and Melinda Gates Foundation and The Global Fund to Fight HIV, TB and Malaria [4]. With a proven track record of introducing new product streams by prequalifying solutions for HIV treatment and diagnosis, and the majority of WHOPQ funding coming from HIV-related donors, the prequalification of digital interventions for HIVST could be taken up by WHOPQ as a way of exploring the introduction of a new SaMD stream.

Improved data quality and interoperability

The International Medical Device Regulators Forum (IMDRF) is a voluntary group of national medical device regulators, chaired by the FDA. IMDRF's objective is to define and standardise medical device registration, and in 2013 they formed the Software as a Medical Device Working Group [18]. This working group initially defined SaMD using standardised vocabulary and then published a framework for risk categorisation, a quality management system and the clinical evaluation of SaMD [18].

These working group documents are supplemented by guidance from the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), independently producing guidance documents for medical devices and software. ISO 13485 and ISO 14971 define the requirements for quality and risk management for SaMD, while ISO 82304 is directly concerned with health apps. Furthermore, IEC 62304 and IEC 62366 address the software lifecycle and usability engineering processes [30,31]. SaMD manufacturers must also consider the Fast Healthcare Interoperability Resources (FHIR) regulations, which outline the ideal rules for collecting and exchanging healthcare data electronically, and the European Union's General Data Protection Regulation (GDPR), which ensures data security and privacy [32,33].

Despite this abundance of guidelines and frameworks, not all regulatory bodies adopt and follow them with the same rigor [34]. A study of nine countries found that most countries had centralised regulatory authorities that use a framework to evaluate health apps [35]. However, these countries had varying oversight of the usability, accountability, and interoperability of the apps [35].

Interoperability is especially important for digital interventions for HIVST, as there is a need to record results for linkage to care and epidemiological tracing. Furthermore, there is a need to standardise how to capture information from emerging populations of HIV testers, including individuals on PrEP and people living with HIV that continue to self-test. However, these indicators are not included or defined in the WHO document recommending HIV self-testing [36]. By prequalifying digital interventions for HIVST, the WHOPQ could consolidate data collection and de-silo interoperability issues. Many UN agencies, NGOs and donors, like the Global Fund, now require WHOPQ for bulk purchasing of medicines and IVDs. Prequalifying digital interventions for HIVST could ensure that data collection and interoperability would be achieved at scale [37].

Concerns regarding prequalification of digital interventions for HIVST

More important digital health priorities

The regulation of SaMD is on the WHO roadmap, and while digital interventions for HIVST could offer a low-risk pilot, there may be more impactful digital interventions to start with. In 2019, the WHO held its first Digital Health Technical Advisory Group meeting, which discussed how a prequalification process could be applied to data analytics, specifically the predictive algorithms used in AI/ML-enabled SaMD [28]. It would be challenging to prequalify a learning algorithm that is constantly changing and adapting. However, these algorithms are already in use and, in some cases, were shown to outperform their human counterparts [38]. AI/ML-enabled SaMD is effective in spotting cancerous tumours through image-based AI algorithms, performing insulin dose calculations for diabetes through AI-enabled decision trees and predicting disease patterns through algorithms developed during COVID-19 [38,39].

Despite these benefits, there are also ethical, privacy and liability risks related to AI/ML-enabled SaMD. An example of an ethical risk is racial bias, found in an algorithm that prevented 50% more Black people from accessing extra care, despite having the same risk level as their White counterparts [40]. In this example, incorrect assumptions in the training data led to bias. In addition, there are also privacy concerns regarding ownership and security of the data used to train the AI models. Furthermore, there are liability implications, especially with emerging algorithms used for diagnosis and treatment in clinical environments, where they may present a substantial risk to people's health and wellbeing [41]. Despite these considerable risks, many AI/ML-enabled algorithms are already being trained and used in healthcare facilities without regulation. Prequalifying these SaMD by the WHOPQ may present a critical opportunity to impact patient outcomes positively.

History of Accelerated Approvals for HIV treatment

In the mid-1980s, zidovudine (azidothymidine, AZT) was approved by the FDA as the first antiretroviral drug for the treatment of AIDS. Despite substantial side effects, AZT effectively reduced mortality and opportunistic infections in AIDS patients, leading to FDA approval in a record 20 months, years faster than traditional medication approvals [42]. In 1986, the AZT clinical trials were stopped after only four months, as there was only one death in the AZT arm versus 19 in the placebo arm. With such strong evidence supporting AZT, the drug manufacturer, Burroughs Wellcome, determined that it would be unethical to continue the trial and delay AZT treatment to the placebo group [43]. For the FDA to fast-track the approval and provide emergent therapies to severely ill patients, new Accelerated Approval Regulations were implemented alongside new Treatment Regulations for Investigational New Drugs. These regulations allowed for removing placebo arms in ARV-related studies to ensure all participants had access to promising life-saving treatments [44].

The same approach could be applied to digital interventions for HIVST. Allowing their use without prequalification may accelerate time to market and increase their impact. With faster access, these promising interventions would guide more people through HIV testing and link more people living with HIV to life-saving ARV treatment. Early access to ARV treatment increases the life expectancy and quality of life of people living with HIV. In addition, there are epidemiological benefits at the population level, as ARV treatment decreases HIV viral load, and when the viral load is undetectable, HIV becomes untransmittable [45]. Furthermore, newly diagnosed people living with HIV change their sexual behaviour after learning their status, leading to increased condom use and fewer sexual partners [46].

Existing barriers to WHOPQ

With almost 26 million people living with HIV, Africa accounts for over two-thirds of the global disease burden of HIV [47]. Despite such a high disease burden, less than 2% (5/297) of the prequalified medications for HIV/AIDS were from African manufacturers; Lamivudine/Zidovudine (Universal Corporation Ltd, Kenya and Aspen Pharmacare Ltd., South Africa), Lamivudine/Zidovudine + Nevirapine (Aspen Pharmacare Ltd., South Africa) and Ceftriaxone, 500mg and 1000mg (Egyptian International Pharmaceutical Industries Company, Egypt). Regarding HIV diagnostics, none of the 62 prequalified IVDs were from African manufacturers, however, one device, the Mylan HIV self-test (Atomo Diagnostics, Australia), has a secondary manufacturing site in South Africa [4].

The cost of research and development for medications and IVDs is a crucial barrier to entry that keeps 98% of these items from being manufactured in Africa [4], however, the obstacles to developing digital interventions are much lower. There are over 7,000 tech start-ups in Africa

and, in 2021, these African start-ups raised over USD 2 billion [48,49]. Most of these start-ups develop fintech and e-commerce platforms, with less than 6% of the total funding going to digital health start-ups [50]. For these digital health start-ups, the cost of USD 31,000 for WHOPQ may be prohibitive, especially considering that the process could keep their product out-of-market for at least one and a half years before the prequalification is completed [24,25].

Conclusion

Access to the market of SaMD is regulated nationally by more than half the WHO member states. However, despite IMDRF, ISO and EIC frameworks, there is no standardised international regulatory board for digital health interventions. The WHOPQ provides regulatory approvals for vaccines, medication and IVD, which could also be used to prequalify SaMD. Digital interventions for HIVST could be considered for a low-risk pilot case, based on the WHOPQ's history with lifesaving HIV interventions and the need to standardise data and interoperability issues. If prequalification of digital interventions for HIVST were to become available, care should be taken to ensure that the process does not inequitably introduce barriers for digital health companies from LMICs, including in Africa, and that the prequalification does not unnecessarily delay access to people testing for HIV.

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CHAPTER 12. General discussion

This general discussion presents the main findings regarding the aim of this thesis, pertaining to these four research questions.

1. Are HIVSTs a usable, acceptable and feasible option to enhance HIV testing services?
2. Can digital interventions be developed and used to compliment HIVST programmes?
3. Can digital interventions for HIVSTs improve health impact?
4. Should digital interventions for HIVST be scaled-up, and if so, how?

After presenting the main findings, their implications towards the future of HIV testing are discussed, including the strengths and weaknesses of the thesis. The need for future research is then discussed, followed by a final conclusion.

Main findings

In chapter 2, we begin to investigate the first research question pertaining to the usability, acceptability and feasibility of HIVSTs. This study aimed to determine the usability of seven HIVST kits among untrained South Africans, and the average UI was high at 93%. Participants correctly interpreted positive and negative results more than 96%, but only correctly interpreted 80% of the weak positive results. Nearly all participants found the devices easy to use (97%), the IFUSs easy to understand (98%) and felt confident using the test unassisted (96%) The major difficulty was obtaining and transferring the specimen, and participants also suggested improvements to packaging/IFUs to further increase usability. The UI and interpretation of results was high and in-line with previous usability studies, suggesting that these kits are appropriate for use in the general, untrained and unsupervised public [1].

Chapter 3 continued to investigate the first research question by conducting a cross-sectional study on the usability, sensitivity and specificity of four HIVSTs, as directed by the WHO prequalification literature. Similar to the first study, the average usability index was high (97%), while the average sensitivity and specificity were 98.2% and 99.8%, respectively. The average usability index, sensitivity and specificity were all comparatively high, and these results corroborate previous usability and performance studies from other regions. These results suggest HIVSTs are appropriate for the South African market and can assist manufacturers with readying their devices for final WHO prequalification evaluation. Additionally, this study also diagnosed 507 (15.1%) HIV-positive participants from the general population, slightly higher than the national prevalence of 13.1% [2].

While the first two chapters demonstrated the usable, acceptable and feasible of HIVSTs, chapter 4 begins to address the second research question. This study investigated whether digital interventions could be used to compliment traditional HIV testing services, before investigating their use with HIVSTs. Participants in the intervention arm received the SmartLink app, which provided HIV-related laboratory results, information, support, and appointment reminders to

engage and link patients to care. After the eight-month follow-up, linkage to care was 48.6% in the intervention arm versus 45.1% in the control. Although these study-wide findings were not statistically significant, the sub-group of youth aged 18 to 30-years did show a statistically significant 20% increase in linkage to care for the intervention group. Youth under 30 years of age have been historically difficult to reach with traditional interventions, and the SmartLink app provides a proof of concept that this population reacts to mobile health interventions that engage patients in HIV care [3].

Chapter 5 continued to present evidence for the introduction of digital interventions for HIVST, by evaluating the increase of technology use due to the COVID-19 pandemic. Out of 405 participants, the lockdown forced 90% to use more technology, and almost all (97%) participants stated they would continue to use technology after the lockdown. Multimedia (53%) and mobile phone content (24%) were both more common sources of COVID-19 than health organizations and professionals (22%). Overall, the mean COVID-19 knowledge score was 8.8 (out of 10), and 335 (82.72%) had adequate knowledge (scored ≥8). Two-thirds of participants stated that they had used their mobile phones for health information before the lockdown, with web searches (27%), social media (14%), and government and institutional websites (13%) serving as their main sources of information [4].

After showing that digital interventions can be used to increase linkage to care for youth in traditional testing services, and that the general population had increased its comfort and use of digital tools during the COVID-19 lockdown, Chapter 6 introduced the Aspect^{TM} HIVST app, our first digital intervention to compliment HIVSTs. This pilot evaluated the usability, acceptability and feasibility of the Aspect^{TM} HIVST app in Johannesburg, where almost all participants (98.7%) found the app easy to use. Some participants experienced difficulties with the self-test process, and the most were related to the IFU (26; 8.7%). To address these difficulties, participants suggested multimedia supplements, additional languages and simplified instructions to improve usability. All invited individuals agreed to participate in the study, with 267 (89.0%) correctly completing all steps and 210 (78.7%) successfully capturing all information on the app. Most errors (26;8.7%) were testing errors and 1 (0.3%) was from the app-sequence. Despite some challenges with IFU interpretation and data capture via the app, this pilot showed that the Aspect^{TM} HIVST app is an acceptable way to upload mobile HIVST results and demographic information to a central database [5].

While the Aspect^{TM} HIVST study demonstrated high usability, acceptability and feasibility, it was conducted in a clinical setting, under HCW observation, and did not investigate the reporting of results in a real-life setting. Chapter 7 investigated the use of the Ithaka app, as a digital intervention to support HIVST by self-reporting results outside a clinical environment. Of 751

participants, 531 (70.7%) logged onto the app, 412 (54.9%) registered, 295 (39.3%) received counselling and 168 (22.4%) self-reported results. Participants strongly agreed that Ithaka was useful and easy to use, specifically that it was easy to upload results. Of the participants that completed the entire self-test journey, most (87.8%) had no challenges, although two people cited perceived data costs, two had difficulty uploading results, and one had language challenges. Despite the small sample size, this study was able to address the second research question and show that an app could be developed and used to compliment HIVST in real-world conditions. Participants were willing and able to self-report results via the app, while also identifying areas of improvement for scaling up [6].

In chapter 8, a new iteration of the Ithaka app was developed and investigated to address the third research question, to see if a digital intervention for HIVST could improve health impact. For this study, a tablet-based version of Ithaka was used to compliment facility-based HIVST to determine whether this could improve testing efficiency. During the four-month pre-implementation period, 14.5% of the clients tested for HIV, compared to 19.9% during the HIVST implementation period; a 25% increase in overall HIV testing. Of the 2278 that used HIVST, 264 (11.6%) were positive, which indicated that facility-based digitally supported HIVST can increase HIV test volume without decreasing the HIV testing yield or requiring a significant increase in staff or space [7].

While the previous chapters presented original research, the remaining chapters summarise and contextualise these findings to investigate the final research question on whether digital interventions for HIVST should be scaled-up, and if so, how. Chapter 9 offered a chronological history of HIVST from the first kit proposal in 1986, to the WHO formally recommending HIVSTs in 2016, and now, almost 100 countries have embraced HIVST into their testing strategies. Despite the increased adoption, HIVSTs present challenges around pre-and post-test counselling, as well as the ability to report results and link users to care, and digital interventions for HIVST have been introduced to address these challenges. Apps like Aspect^{TM} and Ithaka have joined dozens of other digital interventions to create a growing body of evidence that has validated the use of digital interventions to mitigate these challenges surrounding HIVST. This evidence is promising; however many studies were pilots with small sample sizes that lacked the standardization of indicators required to aggregate data across platforms to prove impact at scale [8].

Although not a HIV-specific study, Chapter 10 examined and evaluated informed consent forms (ICFs), which are of growing importance in research, especially for digital interventions for HIV, where data privacy concerns are large. A total of 75 consent forms were investigated from 35 individual research studies conducted in South Africa, and all of them had been approved by an

academic ethics committee. For the Flesch Reading Ease score, only 25% of the ICFs had easy or standard readability, 31% of the Flesch-Kincaid Grades were grade 8 reading level or lower and only 5% of the SMOG scores were below grade 8 level, which meant that two-thirds of the ICFs fail to meet the South African readability standards. Readability can and should be improved with simple techniques, like keeping sentences short (below 15 words), with mostly one- and two-syllable words, while also ensuring that readability is actively monitored and enforced [9].

Chapter 9 suggested that digital interventions for HIVST should be scaled-up, and chapter 10 emphasized the need to ensure that informed consent is simple to understand for all populations, then Chapter 11 introduced the WHO Prequalification Programme (WHOPQ) as a path to scale-up and standardisation through regulation. The WHOPQ is an international regulatory body that approves vaccines, medications, and in vitro diagnostics, for low-and middle-income countries that do not have the capacity to do their own approvals. Digital interventions for HIVST are a type of software as a medical device (SaMD), and there is currently no standardised system for regulating or approving these interventions, so this article explored whether WHOPQ could be used to prequalify digital interventions for HIVST. The arguments for regulation include the WHOPQ's strong history with HIV, trends in digital health and improved data interoperability. Arguments against prequalification included a stronger need to regulate more sophisticated AI/ML-enabled SaMDs first, a history of accelerated approvals for HIV treatments and existing barriers to WHOPQ. If the WHO begins to prequalify digital interventions for HIVST, it would standardise the interventions and provide a platform for scale-up, however, they must consider accessibility for digital health companies from Africa and ensure that prequalification does not delay access to people testing for HIV [10].

Implications

This section summarises the impact and implications of the main findings discussed above. The impact describes the realised effects of the six original research studies included in this dissertation, while the implications provide context to the main findings, both in South Africa, then internationally.

Impact

More than 8,300 people were given access to HIV testing services through the HIVSTs distributed during the studies included in this dissertation. This led to over 6,000 people learning their HIV status, including 1,173 people that discovered they were HIV positive, and 400 that started life-saving ARV treatment (Table 1) [1-3,5-7].

TABLE 1. Dissertation impact by chapter

	Access to HIVST	Completed HIVST	HIVST positive	Started ART
Ch.2 HIVST usability	1,400	-	-	-
Ch.3 HIVST performance	3,600	3,367	507	-
Ch.4 SmartLink RCT	-	-	345	216
Ch.6 Aspect™ evaluation	300	267	43	-
Ch.7 Ithaka usability	751	168	14	-
Ch.8 Ithaka efficiency	2,278	2,267	264	184
Totals	**8,329**	**6,069**	**1,173**	**400**

ART – antiretroviral therapy; Ch – chapter; HIVST – HIV self-test; RCT – randomly controlled trial.

Furthermore, the author has continued to apply the knowledge developed during this dissertation into the scale-up of digital interventions for HIVST with Aviro Health, the company that developed the Ithaka platform. From February 2021 until May 2023, the author worked with Aviro Health as a health researcher and data scientist to develop and launch the Aviro Pocket Clinic, a scaled-up evolution of the Ithaka platform. The Aviro Pocket Clinic was launched in February 2022, and in just over one year, it has provided access to HIV testing services to over 25,000 people in sub-Saharan Africa through programmes in South Africa, Kenya and Eswatini (Figure 1). Over 23,000 people have used the app to reported self-test results, which has led to almost 2,000 people learning their HIV positive status, and 1,694 of them have begun life-saving ARV treatment [11]. While this case study offers an example of how digital interventions for HIVST can mature, the actual impact of these interventions is much larger if can truly reach scale.

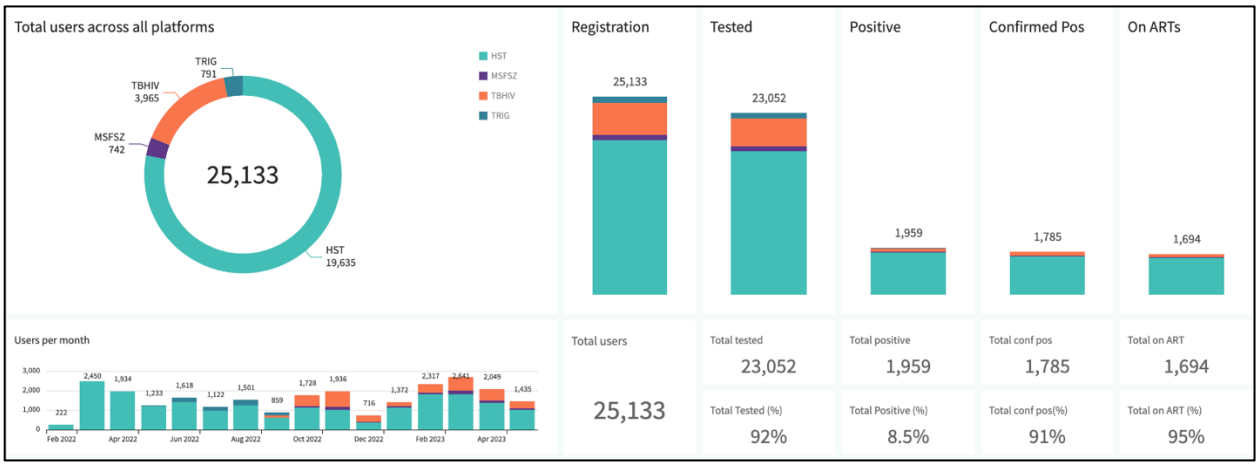

FIGURE 1. Aviro Pocket Clinic HIVST cascade from their internal dashboard

Implications of digital interventions for HIVST in South Africa

In December 2020, UNAIDS updated their 90-90-90 targets to 95-95-95, even though the COVID-19 pandemic slowed progress, resulting in only 14 countries achieving the initial 90-90-90 targets

[12]. Despite strong efforts and universal test and treatment programmes, South Africa was one of the many countries that fell short of the initial 90-90-90 targets. As of July 2022, 94% of South Africans living with HIV knew their status, but only 78% of them were on ARVs, and 89% of them achieved viral suppression [13].

Although the testing numbers have almost reached the 95% target, there is still a large gap with linkage to care, especially in key populations like males and youth, where their linkage to care is at 72% and 69%, respectively. Even with testing, where the national average is approaching the target, there are large regional disparities, as communities in the Free State are testing well above 90%, but farming communities in the Northern Cape are only at 56%. Innovative new techniques are needed to close these gaps, especially in key populations, and this dissertation has provided evidence that digital interventions for HIVST are well positioned to help close these gaps in South Africa [12,13].

Before this dissertation began, HIVSTs had already been championed as one of these new innovations to close the global testing gap, as HIVSTs can complement traditional HIV testing programmes by removing barriers related to stigma and the time required to access traditional testing, especially for those key populations [8]. Despite this knowledge, most of the studies on HIVSTs came from developed countries, so little was known about their feasibility in LMICs. The usability and performance studies presented in chapters 2 and 3 were the first of their kind to present evidence for HIVST in a LMIC, South Africa [1,2].

These studies confirm that HIVSTs are a viable and acceptable option for South Africans looking to privately conduct an HIV test, and with the recent availability of the Mylan HIVST for just USD1, self-test programmes in South Africa are well positioned for an economically viable scale-up [8]. South Africa has introduced self-testing into their national HIV strategy, so the scale-up of self-testing will be an integral component to ensure that the remaining 150,000 South Africans living with HIV become aware of their status to reach the 95%. However, the introduction of self-testing alone will not address the gap in the second 95, which currently represents 1.5 million South Africans [14].

Chapter 9 chronicled the rise of HIVSTs, but it also investigated the challenges they introduce, by providing testing services independent of a healthcare facility [8]. With HIVSTs alone, users may not have access to appropriate counselling, or be able to report results and link to care, which may inadvertently increase the gap in the second 95. Digital interventions for HIVST have been hypothesized as a way to mitigate this risk, which is what chapters 4 through 8 investigated. Chapter 4 showed that lay-persons in South Africa, with no previous knowledge of digital health, were able to successfully use digital technologies to facilitate linkage to care after traditional

testing, then chapter 5 suggested that the COVID-19 lockdown has further accelerated lay-person's comfort with digital technologies. Chapter 6 then showed that a specific digital intervention could be adapted from traditional testing, and modified to compliment self-testing, under observation in a clinical setting. Next, chapter 7 investigated the use of the Ithaka app, as a digital intervention to support HIVST by self-reporting results outside a clinical environment, showing that digital interventions for HIVST could be used to compliment HIVST in real-world conditions [3-6].

After showing that these digital interventions were usable, acceptable and feasible, the investigation turned to effectiveness, where chapter 8 showed that the introduction of digital interventions for HIVST could increase testing efficiency by 25% [7]. These findings suggest that digital interventions for HIVST have the potential to decrease the gap in the second 95 by providing linkage to care to populations that may not have had access to conventional facility-based testing services. The digital interventions investigated during this dissertation have been used to link 400 South Africans living with HIV to care. This sample serves as a proof of concept, but to make a measurable impact on the 1.5 million South Africans that still need to be linked to care, these interventions need to be scaled-up, especially for key populations.

Implications of digital Interventions for HIVST internationally

Similar to South Africa, the global HIV response did not meet the 90-90-90 targets, however the distribution of gaps was different, resulting in different priorities internationally. By the end of 2020, when the initial 90-90-90 goal was expected to be achieved, only 84% of people living with HIV knew their HIV-positive status, 87% of the known positives were on treatment, and 90% of those on treatment had attained viral suppression [12]. The global priority is still the around testing, which is 11% short the new 95% target, followed by linkage to care, which is currently sitting 8% below its new target as well. As described in the South African context, this dissertation has developed a compelling body of evidence for the use of digital interventions for HIVST to close both of these gaps.

While the studies included in this dissertation were conducted in South Africa, the participating populations represented similar demographics seen in other LMICs, especially in sub-Saharan Africa, which implies that the findings can be extrapolated out to similar settings. The 40 countries (including South Africa) that make up Sub-Saharan Africa are often grouped together for reporting, and with over 25 million people living with HIV, the region represent more than two-thirds of the global HIV burden [15]. Within this population, 32% have still not been linked to care, representing a gap in the second 95% of more than 8 million people that could benefit from digital interventions for HIVST to help them access the care they need.

In sub-Saharan Africa, key populations account for half of the new HIV infections each year, but in other regions like eastern Europe and central Asia and the Middle East and North Africa, 95% of new infections are experienced by key populations [14]. These key populations, like men and young people below the age of 24, are much harder to engage for testing and linkage to care [16], and as a result they represent much larger gaps in the testing and treatment targets.

In sub-Saharan Africa, one study showed that the proportion of men who knew their HIV status was 10% lower than that of women, and globally, only 68% of men living with HIV are linked to care, compared to almost 80% for women living with HIV [12]. Men have been well represented throughout this dissertation, especially in chapters 2,3 and 5, where they made up 55% of the study participants. This large sample of men willing to participate in these studies suggests that if digital interventions for HIVST can be scaled-up, they will be accepted by men and may play an integral role in closing their testing and linkage to care gaps [1,2,5].

Men do not access traditional testing services due to barriers associated with fear of stigma and time to access care, and digital interventions for HIVST offer the ability to test independent of traditional facilities, which may remove these barriers. This was reiterated by a 30 year-old man from chapter 2, who stated that *"home test is easier and less scary compared to clinic".* Furthermore, technology and innovative tools tend to be favorably adopted by men, which suggests that digital interventions would be well received, again increasing the likelihood that they test and link to care [17].

Comparable to the differences seen between genders, a similar, but wider gap can be seen across age groups for linkage to care. Young adults under the age of 25, experience a linkage to care rate of only 55% compared to 75% among those over the age of 25 [12]. Similar to males, youth have a higher affinity to technology, and in some sub-Saharan Africa populations, youth are almost 20% more likely to access the internet via their phones than their parent's generation. This was demonstrated in chapter 4, where youth who used the digital intervention had a 20% higher linkage to care rate than those who received traditional care and in chapter 8 where the use of the digital intervention almost doubled the number of youth under 35 diagnosed with HIV [3,7].

The above implications only focused on outcomes at the patient level, but the ability to digitise testing results also has implications on the national level. Chapters 6 and 7 demonstrated that results could be uploaded to a centralised database, which would allow for the real-time monitoring of testing trends, and the ability to identify opportunities to optimise programmatic reach [5,6]. This dissertation also had implications on the international level, as the data generated from the studies in chapters 2 and 3 were used by two HIVST kits, OraSure and INSTI

to be prequalified by the WHO [1,2]. Furthermore, chapter 10 exposed a neglected gap in the readability of consent forms, including those for digitally assisted HIVST, then chapter 11 calls for the WHO to investigate the prequalification of digital interventions for HIVST, to ensure that they are appropriately scaled up and regulated to reach their full, ethical potential [9,10].

Strengths and limitations

One major strength of this dissertation was its thorough and systematic approach where the findings from one study informed the motivation for the next. Instead of just developing and launching a digital intervention for HIVST to see if it worked, the methodical approach ensured that tiered hypotheses were verified before moving onto the next one. This started with the usability, acceptability and feasibility of the self-tests themselves in chapter 2, and once they were deemed appropriate, chapter 3 investigated their performance to determine if their results were accurate. Once chapter 4 determined that digital interventions could be used to link patients to care after traditional testing, chapter 6 investigated the use of a digital intervention for HIVST, under HCW observation at a clinical setting. Chapter 7 investigated the usability of a digital intervention for HIVST independent of a HCW, then chapter 8 showed that an updated version of that digital intervention for HIVST could create a beneficial health impact by improving testing efficiency. Chapter 9 then summarised the evolution of digital interventions for self-testing, then chapter 11 explored their future by calling for regulation through WHO Prequalification [1-3,5-8,11].

The methodical approach also ensured that a large sample size of over 8,300 participants got to experience a seven different HIVST kits and four different digital interventions. With such a variety of HIVST kits and digital interventions, we ensured that a strong body of evidence was created for the HIVST kits and digital interventions, in general, instead of just examining one specific option under a microscope. This should allow the findings to be extrapolated out to inform the development and use of not just the evaluated HIVST kits and digital interventions, but for similar ones not included in the is study as well. There was, however, a weakness created by this approach, as the use of different HIVST kits and digital interventions to create broad, generalised results negated the ability to create detailed body of evidence for one specific HIVST kit used with one digital intervention. The sample size and resources available to the investigation and development of each HIVST kits or digital interventions were dispersed throughout, resulting in much less power for each of the specific kits and interventions under investigation. As a result, this dissertation presented a number of viable proof of concepts, however, none of them were able to prove impact at scale [1-3,5-7].

Another weakness to this thesis was that Chapter 5 on the increased technology uptake during COVID-19, and chapter 10 on the readability of consent forms included data from a broader

sample than just the users of HIVST and digital interventions for HIVST. In order to include significant sample sizes for analysis, the authors had to cast a wider net, however these studies were both still conducted with South African populations, and the readability study did specifically include consent forms for both HIVST and digital interventions for HIVST [4,9].

A selection bias may have been created with convenience sampling used for the first two studies, as well as the mobile phone and digital literacy eligibility criteria needed to participate in the digital interventions studies. Furthermore, all the studies were conducted in the same region of Johannesburg, South Africa. While this ensured that each of the participant populations had comparable demographic distributions throughout the different studies, it also introduced a weakness. Each of these studies were conducted in series to ensure that there was no cross-contamination, however the people from the community may have become more aware of HIVST and the use of digital interventions by the time participants from the last study were selected [1-3, 5-8].

For data collection, there is no validated or standardized usability test for HIVSTs or digital interventions for HIVST, so the questionnaires and indicators developed and analysed to quantify usability only allowed for each device to be evaluated independently. No direct comparisons between products could be made, as a result of different components not being standardized across kits and interventions. For example, there was no universal standard for intensity of a weak positive used to test readings of contrived results. Despite this weakness, chapters 2 and 3 followed the WHO Technical Specification Series for the prequalification of HIV self-test devices, so the usability, sensitivity and specificity results were used to inform the WHO prequalification process for two of the included HIVST kits [1,2].

Future research

As introduced in the Limitations section above, there are three main areas for future research regarding the use and digital interventions for HIVSTs; introduce regulations for standardisation, prove impact at scale, show economic efficiency.

Chapter 10 reviewed the WHO prequalification programme, and presented it as a viable option to regulate digital interventions for HIVST. The WHO prequalification programme already has a strong history with lifesaving HIV interventions, and prequalification could guide the standardisation of data and interoperability issues, while also monitoring the readability of consent forms. If the prequalification of digital interventions for HIVST were adopted, research will be needed to develop the requirements guidelines, build evidence to ensure that participating digital interventions meet said guidelines, then to monitor and evaluate the digital interventions after prequalification [10].

Regardless of whether digital interventions for HIVST are approved for WHO prequalification, there is an immediate need to monitor and evaluate these digital interventions, especially as they are scaled up. There is already a large body of evidence to support these digital interventions for HIVST, however many of them (including the ones from this dissertation) have relatively small sample sizes and implementation periods [5-7]. The time for new pilot studies and proof-of-concepts is over; future studies must focus on the scale-up of digital interventions for HIVST to prove their impact at scale. For this to happen, sample sizes must grow from hundreds of users to hundreds of thousands of users, and programmes must be allowed to run for years, instead of months. Additionally, these studies should have larger implementation footprints. This will ensure that substantial sample sizes are achieved, while also guaranteeing a diverse sample population, to negate the selection biases experienced in the smaller proof-of-concept studies.

In order to determine which digital interventions for HIVST should be championed for scale-up, future studies should also introduce a new set of indicators related to the economic efficiency of programmes that include digital interventions for HIVST. If evidence can be captured that shows the cost-savings created by implementing digital interventions for HVIST, then an argument for scaling specific interventions can be made. In a 2019 study, Phillips et al concluded that if the cost-per-HIV diagnosis is below US$315, then the testing intervention will have an incremental cost-effective ration below US$500 per disability adjusted live year averted, which is the threshold for determining whether a traditional HIV testing service is cost effective [18]. Future studies should include economic indicators to allow comparisons against this threshold.

While future studies considering digital interventions for HIVST, should focus on regulation, scale-up and economic evaluations, their learnings can be applied elsewhere too. Digital interventions for HIVST are currently being used to close the gaps of the first two 95-95-95 targets, but if patients are comfortable entering the care cascade digitally, then these interventions could also be used to close the third 95, and ensure that patients remain adherent to ARVs. Additionally, the lessons learned here could also spawn future research in parallel fields of study. Self-testing has been normalized during COVID-19, and it is currently being used to test and monitor a variety of other disease verticals. There are blood-based self-tests for sexually transmitted infections like hepatitis C and syphilis, and self-sampling is also used to monitor blood-sugar for diabetics [19]. Future research could investigate whether user journeys developed and used by digital interventions for HIVST could be tailored and used to compliment self-testers in these other disease verticals as well.

Conclusion

The studies presented in this dissertation investigated the use of HIVSTs to compliment traditional HIV testing services, and whether digital interventions could be introduced to optimise these HIVST programmes. While HIVSTs were deemed accurate, usable and acceptable by participants from the general population of Johannesburg, HIVSTs also introduced challenges around counselling, reporting results and linkage to care. Digital interventions have been developed to compliment HIVST programmes, and this dissertation has shown that these interventions are not only useable and accepted by participants, but that they could also improve the efficiency of testing programmes. With nearly 100 countries currently endorsing HIVSTs in their national HIV strategy, digital interventions for HIVST should be scaled-up to prove their impact at scale, and WHO prequalification would help standardise and promote their increased use.

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Summary

Globally, there are almost 39 million people living with human immunodeficiency virus (HIV) and with 25 million people living with HIV, the majority of the disease burden is in sub-Saharan Africa. There is no cure for HIV, but anti-retroviral therapy (ART) can be taken by people living with HIV to repair the immune system and prevent transmission of the virus. ART benefits have led to the UNAIDS global HIV 95-95-95 strategy, where 95% of people living with HIV know their status, 95% of known people living with HIV are linked to treatment for ART, and that 95% of those on ART are virally suppressed, by 2030. Globally, we are sitting at 84-87-90, with large gaps in testing and linkage to care. To close these gaps, innovative new testing approaches are needed to expand access to testing and linkage to care, especially for key populations.

HIV self-testing (HIVST) allows a person to test independent of a healthcare facility, and HIVST has been championed as one of these innovative new methods. The move away from facilities may remove barriers around stigma and facility access, however, this may also introduce challenges regarding counselling, reporting results and linkage to care. Digital health tools are being used to optimise care for many disease verticals, and digital interventions for HIVST are being developed to address the challenges associated with HIVST.

The studies presented in this dissertation investigate the use of HIVSTs and whether digital interventions could be introduced to optimise these HIVST programmes, by examining four research questions:

1. Are HIVSTs a usable, acceptable and feasible option to enhance HIV testing services?
2. Can digital interventions be developed and used to compliment HIVST programmes?
3. Can digital interventions for HIVSTs improve health impact?
4. Should digital interventions for HIVST be scaled-up, and if so, how?

Chapter 2 investigated the first research question by evaluating the usability of seven HIVST kits among untrained South Africans. Usability was high, with 97% reporting the devices were easy to use, 96% correctly interpreted positive and negative results, and an average usability index of 91%. These results were in-line with previous usability studies, suggesting that these kits are appropriate for use in the general public.

Chapter 3 continued to address the first research question with a cross-sectional study on the usability, sensitivity and specificity of four HIVSTs, with guidance from WHO prequalification programme. Again, the average usability index was high (97%), as were the sensitivity (98.2%) and specificity (99.8%) of the test kits, which substantiate previously published usability and performance studies. These results suggest that HIVSTs are suitable for the South African market. Furthermore, manufacturers can include these results as evidence for final WHO prequalification evaluation.

For the second research question, chapter 4 investigated whether digital interventions could compliment traditional HIV testing services, before considering their use with HIVSTs. Participants received the SmartLink app, which provided HIV-related lab results and support for linkage care. Linkage to care rates were similar for those who used SmartLink (48.6%) versus the control (45.1%), however, youth under 30-years old, showed a statistically significant 20% increase in linkage to care for SmartLink users. Youth have historically been difficult to reach with traditional interventions, and this study provided a proof of concept that digital health interventions could engage young patients into HIV care.

Chapter 5 builds on this by investigating the impact of the COVID-19 lockdown on technology uptake by South Africans. Analysis of an online survey revealed that the lockdown forced 90% to use more technology, and that multimedia (53%) and mobile phone content (24%) were both more common sources of COVID-19 than directly from health organizations and professionals (22%). Furthermore, two-thirds of participants stated that they had used their mobile phones for health information, suggesting that digital health tools are becoming commonly accepted and adopted by the general population in South Africa.

After showing that digital interventions for traditional testing services could increase linkage to care for youth, and the increasing adoption of digital tools, Chapter 6 investigated, our first digital intervention to compliment HIVSTs. This pilot evaluated the usability, acceptability and feasibility of the Aspect™ HIVST app, and almost all participants (98.7%) found the app easy to use. Despite some challenges with IFU interpretation and data capture via the app, this pilot showed that the Aspect™ HIVST app is an acceptable way to capture demographic information and upload mobile HIVST results to a central database.

Although the chapter 6 study demonstrated high usability, acceptability and feasibility, it was conducted in a healthcare facility, under observation by a healthcare worker. Chapter 7 investigated the real-life use of an app, Ithaka, as a digital intervention to support HIVST by self-reporting results outside a clinical environment. Of 751 participants, 531 (70.7%) logged onto the app, 412 (54.9%) registered, 295 (39.3%) received counselling and 168 (22.4%) self-reported results. Participants strongly agreed that Ithaka was useful and easy to use, specifically that it was easy to upload results. Participants were willing and able to self-report results via the app, which demonstrated that an app could be developed and used to compliment HIVST in real-world conditions.

For the third research question, chapter 8 developed an updated version of the Ithaka app to see if a digital intervention for HIVST could improve health impact. The tablet-based version of Ithaka was introduced into a facility-based HIVST programme to determine whether it could improve

testing efficiency. During the *Ithaka for HIVST* implementation period, 19.9% of clinic visitors tested for HIV, compared to only 14.5% during the four-month pre-implementation period. This 25% increase testing showed that facility-based digitally supported HIVST can increase HIV test volume without requiring a significant increase in staff or space.

Chapters 9 summarised and contextualised the findings from the previous chapters to investigate the final research question on whether digital interventions for HIVST should be scaled-up, and if so, how. Despite the increased implementation of HIVSTs, they still present challenges around counselling, reporting results and linkage to care, and digital interventions for HIVST were developed to address these challenges. Apps like Aspect^{TM} , Ithaka and others have validated the use of digital interventions to compliment HIVST. Although this evidence is promising, most studies were pilots with small samples that lacked standardised indicators across platforms needed to prove impact at scale.

Chapter 10 took a deep dive into informed consent forms (ICFs), that are of particular concern when dealing with sensitive health data like HIV status. Although the South African ethics guidelines suggest that the complexity of ICFs, should be equivalent to the grade 8 reading level or lower, however only one-third of the ICFs examined in this study met this threshold. Readability and should be improved with simple techniques, like keeping sentences short (below 15 words), with mostly one- and two-syllable words, while also ensuring that readability is actively monitored and enforced.

Chapter 11 suggested a path to scale-up, standardisation and regulation by introducing the WHO Prequalification Programme (WHOPQ), an international regulatory body. Digital interventions for HIVST are a type of software as a medical device (SaMD), with no standardised regulation, so this article investigates whether WHOPQ could be used to regulate digital interventions for HIVST. Arguments for regulation included the WHOPQ's strong history with HIV, trends in digital health and improved data interoperability, while arguments against prequalification included a stronger need to regulate AI/ML-enabled SaMDs first and existing barriers to WHOPQ. If the WHO begins to prequalify digital interventions for HIVST, it would standardise the interventions and provide a platform for scale-up, however, they must consider accessibility for digital health companies from Africa and ensure that prequalification does not delay access to people testing for HIV.

Samenvatting

Samenvatting

Wereldwijd leven er bijna 39 miljoen mensen met het humaan immunodeficiëntievirus (hiv) en, met 25 miljoen mensen met hiv, bevindt het grootste deel van de ziektelast zich in Afrika bezuiden de Sahara. Er is geen genezing voor hiv, maar antiretrovirale therapie (ART) kan worden gebruikt door mensen met hiv om het immuunsysteem te herstellen en de overdracht van het virus te voorkomen. Deze positieve effecten van ART hebben geleid tot de wereldwijde UNAIDS 95-95-95-hiv strategie, waarbij 95% van de mensen met hiv hun status kent, 95% van de mensen met bekende hiv-infectie ART gebruikt, en in 95% van degenen die ART gebruiken hiv effectief onderdrukt wordt. Wereldwijd zitten we op 84-87-90, met grote hiaten in hiv-testen en koppeling aan zorg. Om deze hiaten te dichten, zijn met name innovatieve HIV test-benaderingen nodig om de toegang tot testen en de koppeling met zorg te verbeteren, vooral voor sleutelpopulaties.

HIV-zelftesten (HIVZT) stelt een persoon in staat om onafhankelijk van een zorginstelling te testen, en HIVZT wordt gezien als een van de benodigde innovatieve nieuwe hiv-test methoden. Hiv-testen buiten zorgsettings kan barrières rondom stigmatisering en toegang tot zorg wegnemen, maar dit kan ook nieuwe uitdagingen met zich meebrengen met betrekking tot counseling, communiceren van testresultaten en koppeling aan verdere zorg. Digitale instrumenten worden gebruikt om de zorg voor veel ziektes verticaal te optimaliseren, en er worden digitale interventies voor HIVZT ontwikkeld om de uitdagingen die HIVZT met zich meebrengt aan te pakken.

De studies die in dit proefschrift worden gepresenteerd, onderzoeken het gebruik van HIVZT en of digitale interventies kunnen worden geïntroduceerd om de HIVZT-programma's te optimaliseren, en hebben betrekking op vier onderzoeksvragen:

1. Zijn HIVST-programma’s bruikbare, acceptabele en haalbare opties om HIV-testen te verbeteren?
2. Kunnen aanvullende digitale interventies worden ontwikkeld en gebruikt om knelpunten van HIVZT-programma’s te verminderen?
3. Kunnen aanvullende digitale interventies de gezondheidsimpact van HIVZT verbeteren?
4. Zouden digitale interventies voor HIVZT moeten worden opgeschaald, en zo ja, hoe?

Hoofdstuk 2 had betrekking op de eerste onderzoeksvraag en beschreef evaluatieonderzoek naar de bruikbaarheid van zeven HIVZT-kits onder ongetrainde Zuid-Afrikanen. De bruikbaarheid was hoog: 97% gaf aan dat de kits gebruiksvriendelijk waren, 96% interpreteerde positieve en negatieve resultaten correct en de gemiddelde bruikbaarheidsindex was 91%. Deze resultaten komen overeen met eerdere bruikbaarheidsonderzoeken, wat suggereert dat deze kits geschikt zijn voor gebruik door het grote publiek.

Hoofdstuk 3 ging verder met het behandelen van de eerste onderzoeksvraag en beschreef een cross-sectioneel onderzoek naar de bruikbaarheid, sensitiviteit en specificiteit van vier HIVST-kits, op basis van het pre-kwalificatieprogramma van de WHO. Ook in dit onderzoek was de gemiddelde bruikbaarheids-index hoog (97%), evenals de sensitiviteit (98,2%) en specificiteit (99,8%) van de testkits, die eerder gepubliceerde bruikbaarheis- en prestatiestudies ondersteunen. Deze resultaten suggereren dat HIVZT-kits geschikt zijn voor de Zuid-Afrikaanse markt. Bovendien kunnen fabrikanten deze resultaten gebruiken als ondersteuning voor de uiteindelijke prekwalificatie-evaluatie van de WHO.

De studie beschreven in hoofdstuk 4 heeft betrekking op de tweede onderzoeksvraag en ging na of digitale interventies een aanvulling kunnen zijn op het bestaande, traditionele hiv-test aanbod, alvorens het gebruik van HIVZT te overwegen. Deelnemers ontvingen de SmartLink-app, die toegang gaf tot hiv-gerelateerde laboratoriumresultaten en ondersteuning bood voor koppeling aan zorg. Percentages koppeling aan zorg waren in het algemeen vergelijkbaar voor degenen die de SmartLink-app gebruikten (48,6%) en de controle (45,1%), maar voor jongeren onder de 30 jaar werd een statistisch significante toename van 20% in koppeling aan zorg gevonden voor SmartLink-gebruikers. Jongeren zijn van veelal moeilijk te bereiken met traditionele interventies, en deze studie leverde *proof-of-concept* op dat digitale gezondheidsinterventies jongere gebruikers beter zouden kunnen betrekken bij hiv-zorg.

Hoofdstuk 5 bouwde voort op dit onderzoek door de impact van de COVID-19-lockdown op de acceptatie van gezondheidstechnologie onder Zuid-Afrikanen te onderzoeken. Uit analyses van een online-enquête bleek dat de lockdown 90% van de deelnemers dwong om meer gezondheidstechnologie te gebruiken, en dat multimedia (53%) en mobiele telefoons (24%) beide vaak gebruikte kanalen voor informatie over COVID-19 waren dan informatie rechstreeks van gezondheidsorganisaties en professionals (22%). Bovendien gaf tweederde van de deelnemers aan dat ze hun mobiele telefoons hadden gebruikt voor het zoeken van gezondheidsinformatie, wat suggereert dat digitale gezondheidstechnologie breed wordt geaccepteerd en gebruikt in de algemene bevolking in Zuid-Afrika.

Nadat we hadden aangetoond dat digitale interventies voor traditionele hiv-testdiensten de koppeling met hiv-zorg voor jongeren zou kunnen vergroten en digitale informatietechnologie breed geaccepteerd is, onderzocht de studie in hoofdstuk 6 onze eerste digitale interventie als aanvulling op HIVZT. Deze pilot evalueerde de bruikbaarheid, acceptabiliteit en haalbaarheid van de Aspect^{TM} HIVZT-app en bijna alle deelnemers (98,7%) vonden de app gebruiksvriendelijk. Ondanks enkele problemen met de gebruiksaanwijzing en het vastleggen van gegevens via de app, toonde deze pilot aan dat de Aspect^{TM} HIVZT-app een acceptabele manier is om

demografische informatie vast te leggen en HIVZT-resultaten mobiel te uploaden naar een centrale database.

Het onderzoek in hoofdstuk 6 liet weliswaar een hoge mate van bruikbaarheid, acceptabiliteit en haalbaarheid zien, maar werd het uitgevoerd in een zorgsetting en onder toezicht van een gezondheidswerker. Het onderzoek in hoofdstuk 7 had betrekking op het gebruik van een app, Ithaka, als digitale interventie ter ondersteuning van HIVZT door middel van zelfrapportage van resultaten buiten een klinische omgeving. Van de 751 deelnemers logden er 531 (70,7%) in op de app, 412 (54,9%) registreerden zich, 295 (39,3%) ontvingen counseling en 168 (22,4%) rapporteerde test-resultaten. De deelnemers waren het er sterk over eens dat Ithaka nuttig en gebruiksvriendelijk was, met name dat het gemakkelijk was om resultaten te uploaden. Deelnemers waren bereid en in staat om zelf hun testresultaten te rapporteren via de app, wat liet zien dat een app kon worden ontwikkeld en gebruikt als aanvulling op HIVST in realistische omstandigheden.

Met betrekking tot de derde onderzoeksvraag werd in de studie beschreven in hoofdstuk 8 een geüpdatete versie van de Ithaka-app ontwikkeld om na te gaan of een aanvullende digitale interventie de gezondheidsimpact van HIVZT zou kunnen verbeteren. De tabletversie van Ithaka werd geïntroduceerd in HIVST-programma in zorgsettings om te bepalen of het de efficiëntie van hiv-testen zou kunnen verbeteren. Tijdens de implementatieperiode van Ithaka voor HIVZT testte 19,9% van de bezoekers van de kliniek op hiv, vergeleken met slechts 14,5% tijdens de vier maanden durende pre-implementatieperiode. Deze toename van 25% in hiv-testen laat zien dat digitaal ondersteund HIVZT in zorgsettings het aantal uitgevoerde hiv-testen kan verhogen zonder dat er een substantiële toename van personeel of spreekkamers nodig is.

In hoofdstuk 9 zijn de bevindingen uit de voorgaande hoofdstukken samengevat en in context geplaatst om de onderzoeksvraag te onderzoeken of digitale interventies voor HIVZT zouden moeten worden opgeschaald en, zo ja, hoe. Ondanks de toegenomen implementatie van HIVZT, gaan deze nog steeds gepaard met knelpunten op het gebied van het aanbieden van counseling, rapportage van resultaten en koppeling aan zorg, en digitale interventies voor HIVZT zijn specifiek ontwikkeld om deze uitdagingen aan te pakken. De bevindingen van onderzoek naar apps zoals Aspect™, Ithaka en andere, ondersteunen het gebruik van digitale interventies als aanvulling op HIVZT. Hoewel de resultaten veelbelovend zijn, waren de meeste onderzoeken slechts pilots met kleine steekproeven en gestandaardiseerde indicatoren op verschillende platforms ontbraken die nodig waren om de impact op grotere schaal vast te stellen.

Hoofdstuk 10 ging dieper in op formulieren voor geïnformeerde toestemming (ICF), die van bijzonder belang zijn bij het omgaan met gevoelige gezondheidsgegevens zoals hiv-status.

Hoewel de Zuid-Afrikaanse ethische richtlijnen aangeven dat de complexiteit van ICFs gelijk zou moeten zijn aan het leesniveau van 8 of lager, voldeed slechts een derde van de ICFs die in dit onderzoek werden onderzocht aan deze drempelwaarde. De leesbaarheid moet worden verbeterd, wat kan met eenvoudige technieken zoals het kort houden van zinnen (minder dan 15 woorden) en het gebruik van voornamelijk één- en tweelettergrepige woorden. Ook moet ervoor worden gezorgd dat de leesbaarheid actief wordt gecontroleerd en gehandhaafd.

Hoofdstuk 11 beschreef een pad naar opschaling, standaardisatie en regulering van digitale HIVZT interventies door de introductie van het WHO Prequalification Program (WHOPQ) voor internationale regulering. Digitale interventies voor HIVZT kunnen gezien worden als een type software as a medical device (SaMD), waarvoor gestandaardiseerde regelgeving ontbreekt. De analyse in hoofdstuk 11 ging na of het WHOPQ gebruikt kan worden om digitale interventies voor HIVZT te reguleren. Argumenten voor regulering waren onder meer de uitgebreide ervating van het WHOPQ met hiv-technologie, trends in digitale gezondheidsintreventies en verbeterde data-interoperabiliteit, terwijl argumenten tegen prekwalificatie onder meer betrekken hebben op het baleng van het eerst reguleren van AI/ML-compatibele SaMDs en bestaande beperkingen van het WHOPQ. Als de WHO digitale interventies voor HIVZT zou willen beginnen te prekwalificeren, zou dat interventies standaardiseren en een platform bieden voor opschaling, maar de toegankelijkheid voor digitale gezondheidsbedrijven uit Afrika moet in het oog gehouden worden, evenals dat prekwalificatie de toegang tot digitale HIVZT technologie niet vertraagd.

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Curriculum Vitae

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Summary of Qualifications

Versatile consultant with 20 years of experience, including over 10 implementing projects and providing solutions in Public Health, utilizing digital resources and research to develop content, prove impact, advise policy and improve health outcomes in diabetes, NCDs, HIV, and TB. Prolific author, adept with presentations, data visualization, technical and academic writing.

Professional Skills

- Public health and digital health in LAMICs
- Developing frameworks and guidelines
- Thought leadership and knowledge transfer
- Data analysis and visualization
- Peer-reviewed research and science writing
- Public-private partnerships, stakeholder management

Professional Affiliations

- UN Kenya Spousal Association
- Project Management South Africa
- Public Health Association of South Africa
- Kenya Diabetes Study Group
- International AIDS Society
- AEMCA-Advanced Emergency Medical Care Ass't

Professional Experience

Senior Consultant | World Bank, USA *08/2023-present*

As a consultant with the World Bank's Digital Health Flagship Program, I have been leading a research initiative that aims to define and quantify the secondary values of digital health to improve the value proposition of digital health interventions and better reflect their true economic impact.

- Developed a new metric, the Digital-DALY, which incorporates secondary benefits of digital health (user benefits, health system benefits, data benefits, cross-sectoral benefits and quality benefits) into a digital score that can be used to adjust the commonly used DALY

Digital Health Consultant | Florida State University, USA *06/2023-present*

At the Institute for Digital Health and Innovation, I am a digital health specialist in sub-Saharan Africa completing a backlog of projects that were stalled at various stages of implementation.

- Recently conducted a scoping review of mobile health interventions for AGYW taking PrEP to identify opportunities for the development and scale-up of digital tools to close existing gaps

- Currently conducting a pilot evaluation of the Vuka+ app, which is intended to help AGYW in sub-Saharan Africa adhere to PrEP

Health Research and Data Science | Aviro Health, South Africa *02/2021-05/2023*

Produced and implemented a new M&E framework, launched live dashboards for the company including a geospatial heatmap, that led to updated company OKRs and programme objectives, and data-informed decisions, resulting in programme improvements that led to hundreds of newly captured HIV positive patients that started treatment and the launch of 2 diabetes products.

- Developed, launched and monitored the original PSI HIVST chatbot with Aviro, including drafting the M&E framework, creating daily dashboards, drafting stakeholder reports and routine monitoring
- Transformed an excel-based data system to an AWS-based system, which created better analysis and the automation of reports for stakeholders, resulting in two key partners renewing their contracts
- Author of 4 peer-reviewed journal articles that show the platform's proven health impact

Digital Health Consultant | Kemet Advanced Pharmaceuticals, Canada *10/2020-01/2021*

Worked closely with CEO to provide business insights to launch startup by researching and drafting business plan, concept note and export development plan, including risk assessments and stakeholder mapping.

- Successfully led Kemet through the Trade Accelerator Program hosted by the Edmonton Chamber of Commerce and World Trade Organization Toronto

Digital Health Project Manager | Wits RHI, South Africa *08/2017-01/2021*

Prime investigator and author for mobile based platforms such as NurseConnect, with the NDOH and SmartLink ARV with the World Bank. Reviewed content submitted by other team members, and crafted proposals for digital and mobile health interventions for Healthcare indicators for HIV and NCDs.

- Produced 12 white-paper publications in peer-reviewed scientific journals. These strong publications enabled the institution to receive government subsidies, while increasing visibility to attract donors
- The published NurseConnect evaluation enabled the programme to be scaled up at national level
- Conducted focus groups with government representatives, technical partners, and nurses, covering 18 public health facilities. Findings among maternal nurses were deployed to all nurses across the country, along with a WhatsApp platform that replaced SMS-messages

Digital Health Consultant | VIA Global Health, USA 03/*2018-10/2018*

Conducted desk reviews to generate market insights and business development strategies. Assembled data dashboards to obtain sound strategy advise for initiatives inside and outside of the organizations.

- Used digital transformation to leverage WhatsApp as an alternative to e-mail sequencing, which yielded four times the usual client uptake
- Designed emerging market entry strategies for clients in the medical device industry

Science Writer | Elizabeth Glaser Pediatric AIDS Foundation, USA *04/2017-02/2018*

Composed articles and reports on HIV peer support, as well as community-based ARV programs. Developed article matrix, literature reviews, and code lists for qualitative data.

- Drafted literature reviews and reports aimed to advise the Cameroon and Mozambique governments on HIV prevention

Paramedic | Peterborough and Northumberland Paramedic Service, Canada *06/2014 to 01/2017*

Evaluate and provide emergency treatment to patients on-site as needed, as well as stabilize while in transit to a medical facility. Ensured all equipment was in optimal conditions at all times. Interacted with other practitioners, appraised them when transferring patients, and prepared detailed medical documentation.

- Two-time judge of the Canadian National Paramedic Competition
- Designed and executed training on medical procedures and laboratory for Fleming College

Education

- **Doctor of Philosophy**, 2024 | Utrecht University, Utrecht, The Netherlands
  - *Digital interventions for HIV self-testing*
- **Master of Public Health**, 2018 | University of Johannesburg, South Africa
  - *Concentration on mHealth for diabetes prevention, and education*
- **Bachelor of Science, Physiology**, 2006 | McGill University, Canada
- **Certificate of mHealth Technologies HIV**, 2017 | University of the Witwatersrand, South Africa
- **Diploma - Paramedic**, 2014 | Fleming College, Peterborough

List of Publications

1. Fischer AE, Lalla-Edward ST, Edward VA et al. Should digital interventions for HIV self-testing be regulated with WHO prequalification? WHO Bulletin. (Under Review; 16/04/2023)
2. Fischer AE, Abrahams M, Shankland L, et al. The evolution of HIV self-testing and the introduction of digital interventions to improve HIV self-testing. Front. Reprod. Health. 2023. 5:1121478
3. Fischer AE, Phatsoane M, Majam M, et al. Uptake of the Ithaka mobile application in Johannesburg, for human immunodeficiency virus self-testing result reporting. S Afr J HIV Med. 2021;22(1), a1197.
4. Fischer AE, Venter F, Collins S, et al. The readability of informed consent forms for research studies conducted in South Africa. S Afr Med J 2021;111(2):180-183.
5. Fischer AE, Van Tonder T, Gumede SB, et al. Changes in Perceptions and Use of Mobile Technology and Health Communication in South Africa During the COVID-19 Lockdown. *JMIR Form Res* 2021;5(5):e25273
6. Fischer AE, Sebidi J, Barron P, Lalla-Edward ST. The MomConnect Nurses and Midwives Support Platform (NurseConnect): A Qualitative Process Evaluation. *JMIR Mhealth Uhealth* 2019;7(2):e11644
7. Fischer A, Chadyiwa M, Tshuma N, et al. Acceptability of mHealth Interventions to Increase Diabetic Risk Factor Awareness Among the Commuter Population in Johannesburg.*JMIR Diabetes* 2019;4(3):e12600
8. Majam M, Fischer A, Reipold EI, et al. A Lay-User Assessment of Hepatitis C Virus Self-Testing Device Usability and Interpretation in Johannesburg, South Africa. *Diagnostics* 2021, 11, 463.
9. Majam M, Fischer A, Phiri J, et al. International citizen project to assess early stage adherence to public health measures for COVID-19 in South Africa. PLoS ONE 2021. 16(3): e0248055.
10. Mash R, Schouw D, Fischer AE. Evaluating the Implementation of the GREAT4Diabetes WhatsApp Chatbot to Educate People With Diabetes During COVID-19. JMIR Diabetes 2022;7(2):e37882.
11. Mshweshwe-Pakela NT, Mabuto T, Shankland L, Fischer A, et al. Digitally supported HIV self-testing increases facility-based HIV testing capacity in Ekurhuleni, South Africa. S Afr J HIV Med. 2022;23(1)
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13. Venter WDF, Fischer A, Lalla-Edward ST, et al. Improving Linkage to and Retention in Care in Newly Diagnosed HIV-Positive Patients Using Smartphones in South Africa. *JMIR Mhealth Uhealth* 2019;7(4)

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15. Gous N, Fischer AE, Rhagnath N, et al. Evaluation of a mobile application to support HIV self-testing in Johannesburg, South Africa. S Afr J HIV Med. 2020;21(1):a1088.
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