An Exploration of Accuracy of HIV Self-Testing with Digital Supports

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Table of Contents

Abstract

Since the start of the epidemic in 1981, the human immunodeficiency virus (HIV) pandemic has impacted the lives of approximately 84 million people worldwide. 42 years later, we are together in fighting the spread of the virus. The epidemic today is concentrated in key populations such as men who have sex with men (MSM), transgender people, people who inject drugs (PWID), and those belonging to the Black and Indigenous people of colour (BIPOC) populations, and the scourge of the pandemic is far from over. The field of HIV is blessed with highly effective treatment options, pre-exposure prophylaxis (PrEP) medications and other prevention strategies, yet we are miles behind in eliminating the virus.

The United Nations Programme on HIV/AIDS (UNAIDS) has set targets to reach HIV elimination by 2030. These targets aim to screen 95% of those who are HIV-positive, treat 95% of those screened, and limit the viral load of 95% of those on treatment. Of these targets, screening individuals affected is the hardest. In recent years, HIV self-testing (HIVST) has become a last mile solution to screen individuals for HIV and its use was amplified in 2016, with WHO's HIVST guidelines.

HIVST is used to increase testing rates and since the pandemic, the process is being improved by the support of digital innovations. Digital supports or innovations are applications (apps), websites, or platforms that simplify the process of testing or interpretation or reporting or linkage. Digital HIVST is a method of increasing serostatus awareness and making HIV testing more accessible for all populations. Due to the novelty of digital HIVST, this field an area of expansion and researching outcomes is crucial to end the HIV epidemic.

Past research has focused on feasibility and if intended users are willing to use digital HIVST methods. Recent literature has focused on efficacy and effectiveness. This alludes to how

much of a difference these supports make in terms of screening uptake, detection of new infections, proportion of those linked to care, and more. HIVST were accurate enough to be approved for use by the Food and Drug Administration (FDA) in 2012, but there is always room for improvement in accuracy, which can be achieved with digital supports.

However, data on the accuracy of the self-tests with digital support have hardly been reported on yet. Improvement in accuracy of testing process, increases faith in the process and reassures the self-tester of the test result. It also encourages and enhances proactivity in decision making for tests. The accuracy component is often ignored with digital supports and is an area where technology can greatly help, which is what this thesis addresses.

Therefore, this thesis encompasses a systematic review and a secondary data analysis that were conducted with the focus of digital HIVST accuracy.

Résumé

Depuis le début de l'épidémie en 1981, la pandémie du virus de l'immunodéficience humaine (VIH) a affecté la vie de quelque 84 millions de personnes dans le monde. 42 ans plus tard, nous luttons ensemble contre la propagation du virus. Aujourd'hui, l'épidémie se concentre sur des populations clés telles que les hommes ayant des rapports sexuels avec des hommes (HSH), les transsexuels, les personnes qui s'injectent des drogues (PWID) et les populations noires et indigènes de couleur (BIPOC), et le fléau de la pandémie est loin d'être terminé. La lutte contre le VIH bénéficie d'options thérapeutiques très efficaces, de médicaments de prophylaxie pré-exposition (PrEP) et d'autres stratégies de prévention, mais nous sommes encore loin d'avoir éliminé le virus.

Le programme des Nations unies sur le VIH/sida (ONUSIDA) a fixé des objectifs pour l'élimination du VIH d'ici à 2030. Ces objectifs visent à dépister 95 % des personnes séropositives, à traiter 95 % des personnes dépistées et à limiter la charge virale de 95 % des personnes sous traitement. De tous ces objectifs, le dépistage des personnes touchées est le plus difficile. Ces dernières années, l'autotest VIH est devenu une solution de dernier recours pour le dépistage du VIH, et son utilisation a été amplifiée en 2016, avec les lignes directrices de l'OMS sur l'autotest VIH.

Les tests de dépistage du VIH sont utilisés pour augmenter les taux de dépistage et, depuis la pandémie, le processus est amélioré grâce aux innovations numériques. Les supports ou innovations numériques sont des applications (apps), des sites web ou des plateformes qui simplifient le processus de dépistage, d'interprétation, de déclaration ou de mise en relation. Le dépistage numérique du VIH est une méthode qui permet de mieux faire connaître le statut sérologique et de rendre le dépistage du VIH plus accessible à toutes les populations. En raison

de la nouveauté des tests numériques de dépistage du VIH, ce domaine est en expansion et la recherche de résultats est cruciale pour mettre fin à l'épidémie de VIH.

La recherche passée s'est concentrée sur la faisabilité et sur la volonté des utilisateurs prévus d'utiliser les méthodes numériques de dépistage du VIH. La littérature récente s'est concentrée sur l'efficacité et l'efficience. Cela fait référence à la différence que ces supports font en termes de participation au dépistage, de détection des nouvelles infections, de proportion de ceux qui sont liés aux soins, et plus encore. Les tests de dépistage du VIH ont été suffisamment précis pour que leur utilisation soit approuvée par la Food and Drug Administration (FDA) en 2012, mais il est toujours possible d'améliorer la précision, ce qui peut être fait grâce aux supports numériques.

Toutefois, les données relatives à la précision des autotests avec support numérique n'ont guère été communiquées jusqu'à présent. L'amélioration de la précision du processus de test renforce la confiance dans le processus et rassure l'autodiagnostiqueur quant au résultat du test. Elle encourage et renforce également la proactivité dans la prise de décision pour les tests. La composante de précision est souvent ignorée avec les supports numériques et c'est un domaine où la technologie peut grandement aider, ce qui est l'objet de cette thèse.

Par conséquent, cette thèse englobe un examen systématique et une analyse de données secondaires qui ont été menés en se concentrant sur l'exactitude des tests numériques de dépistage du VIH.

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Ashlyn Beecroft

Contributions of Authors

This thesis was designed and written by Ashlyn Beecroft.

This thesis was reviewed by Dr. Nitika Pant Pai.

Work presented in the first and second manuscripts of this thesis will be submitted for publication.

The contribution of authors for the first manuscript are as follows:

Ashlyn Beecroft wrote the initial introduction, results, and discussion sections of the manuscript. She also conducted the search and data review.

Olivia Vaikla wrote the initial methods section of the manuscript, as well as reviewed data.

Dr. Nitika Pant Pai reviewed and edited the manuscript.

The contributions of authors for the second manuscript are as follows:

Ashlyn Beecroft wrote the initial manuscript, as well as conducted the statistical analysis using Stata software.

Olivia Vaikla reviewed and edited the manuscript.

Dr. Aliasgar Esmail, Dr. Keertan Dheda, and Dr. Nitika Pant Pai designed and conducted the original trial from which data for the analysis was collected.

The following are thesis committee members who provided guidance and support through the thesis writing process, as well as reviewed final versions of the manuscripts:

Dr. Thomas Duchaine

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List of Figures + Tables

Manuscript 1

Appendix

Manuscript 2

List of Abbreviations

ACB: African, Caribbean, and Black

AIDS: acquired immunodeficiency syndrome

Apps: applications

ART: antiretroviral therapy

CAHR: Canadian Association for HIV Research

CDC: Centres for Disease Control

CI: confidence interval

CVCT: couples voluntary counselling and therapy

DVM: digital vending machines

ELISA: enzyme-linked immunosorbent assay

FDA: Food and Drug Administration

FIND: Foundation for Innovative New Diagnostics

HIV: human immunodeficiency virus

HIVST: HIV self-test / self-tests / self-testing

IAS: International AIDS Society

IDSA: Infectious Diseases Society of America

LICs: low-income countries

MC: medical circumcision

MSM: men who have sex with men

NOS: Newcastle-Ottawa Scale

NPV: negative predictive value

PEP: post-exposure prophylaxis

PLWH: people living with HIV

PPV: positive predictive value

PrEP: pre-exposure prophylaxis

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PWID: people who inject drugs

RCT: randomized control trials

RNA: ribonucleic acid

RoB2: Cochrane Risk of Bias Tool 2

RR: Risk ratio

SD: standard deviation

SMS: short messaging service

Sp: specificity

Sn: sensitivity

SW: sex workers

UNAIDS: Unites Nations Programme on HIV/AIDS

US: United States

WHO: World Health Organization

Chapter I: Introduction

In 1981, the world was struck with a pandemic that influenced the lives of millions [1]. Although men who have sex with men (MSM) were primarily affected in the beginning of the pandemic, it soon spread to the general population. Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) swept the globe and even decades later, still take the lives of approximately one million people every year [2].

The HIV pandemic impacts 38.4 million individuals who are living with the virus [3]. To combat the high rates of HIV infection worldwide, The Joint United Nations Programme on HIV/AIDS (UNAIDS) previously set a 90-90-90 target for 2016 and has since updated the target to 95-95-95 to be reached by 2025, to end HIV transmission by 2030 [4]. UNAIDS targets imply that to end the virus, we need 95% of those who are infected to know their status, 95% of those who know their status should be on antiretroviral therapy (ART), and 95% of those on ART should have significantly suppressed viral loads [4].

Although some countries have successfully met these targets, such as Botswana, many are still struggling to reach the first 95% target [5]. Part of the struggle in meeting these targets entails addressing the sociopolitical problems of reducing HIV-related stigma and discrimination, promoting human rights and social justice, decriminalizing HIV serostatus, improving laws, and strengthening healthcare systems to improve community engagement in HIV prevention and care.

The first target emphasizes the importance of HIV testing and diagnosis, as it aims to ensure that 95% of people living with HIV are aware of their HIV status [4]. This requires scaling up HIV testing services, implementing innovative testing strategies, and promoting HIV testing as a routine part of healthcare services. It also involves reaching key populations who may face

barriers to accessing testing and diagnosis and offering them convenient solutions at their preferred venues of choice.

The second target focuses on ensuring that 95% of people diagnosed with HIV have access to and are receiving long-term ART. ART is a cornerstone of HIV treatment, as it suppresses the proliferation of the virus, therefore reducing HIV-related morbidity and mortality, and preventing viral transmission [6]. Achieving this target involves expanding access to ART, improving linkage to care and treatment initiation, and addressing barriers to adherence to ART and maintaining retention in care of positive individuals on ART.

The third target aims to ensure that 95% of individuals receiving ART achieve viral suppression. Viral suppression occurs when the level of HIV in a person's blood is undetectable, greatly reducing the risk of HIV transmission [7]. It also contributes to improved health outcomes for people living with HIV. This target requires ensuring optimal adherence to medicinal treatment, regular monitoring of viral load, and providing support services to address factors that may impact adherence and viral suppression.

A diagnosis of HIV today is not a death sentence. ART treatments are highly effective and have saved the lives of millions of individuals worldwide. Newer prevention options such as pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), medical circumcision (MC), and couples voluntary counselling and therapy (CVCT), are also recommended by UNAIDS, CDC, PHAC, and have been life-saving [8, 9, 10]. The challenge today is to provide these options to individuals at high risk of contracting HIV and to keep HIV in check. An innovative method that appeared first in 2012 and has been a game changing innovation in the field of infectious diseases, is HIV self-testing (HIVST). It is a promising method of increasing serostatus awareness and reaching the UNAIDS goal by 2025. HIVST involves both oral- and blood-based

self-sampling and testing methods that individuals can perform on their own, without the assistance of a healthcare professional. The benefits of HIVST include convenience, accessibility, quick results, and a promise of rapid linkages to care.

Self-testing can greatly aid expansion and access to testing services, particularly for individuals who may be hesitant to visit a healthcare facility because of the risk of stigma or discrimination. HIVST allows people to test for HIV in the privacy of their own homes or other preferred settings, at a time that suits them best. Kits can be bought like other forms of over-the counter healthcare services at facilities such as pharmacies, community-based organizations, and online. The kits include instructions that guide the user through the self-testing process so they can understand how to conduct the test.

HIVST produces a result in approximately 20 minutes, therefore allowing the individual to know their result quickly and not have to be waiting for days waiting to hear from a clinic that may never call. With HIVST linkage to care is crucial, as an offer of a self-test does not involve a healthcare practitioner involved and therefore the user must initiate continuative care if needed. While the privacy and autonomy associated with self-testing are very valuable, especially given the stigmatized nature of a disease such as HIV, it does leave patients to fend for themselves.

A potential solution to fill this gap in proactive care seeking is the integration of digital health systems, which are defined by the World Health Organization (WHO) as the use of digital innovations such as mobile phones or other wireless technologies to assist in health outcome successes [11]. Digital innovations in self-testing have the potential to revolutionize the support and linkage to care provided to individuals undergoing the self-testing process. Unlike traditional self-testing methods, digital interventions can offer unique and personalized forms of support that may not be readily available otherwise. For these reasons, it is important to summarize the

existing research that has been focused on the role digital interventions play in the HIVST process.

As well, due to the novelty of digital supports being used with HIV self-tests, their accuracy has not been thoroughly analyzed to date. The assumption behind this is that these self-tests have been accurate enough, rated at 98% sensitivity and 99% specificity, but there is a drop in sensitivity at the hands of a lay end-user. The Food and Drug Administration (FDA) approved oral-based HIV self-tests in 2012, reporting their sensitivity as 92%, considering the need to provide these tests to the general population superseded arguments related to increases in accuracy [12]. However, accuracy arguments are important to address again in 2023, due to the proliferation of digital supports and the potential of these supports to improve accuracy, the use of image analyses, and machine learning in the near future of diagnostic performance.

There is also a need to revisit evidence supporting the improvements in diagnostic performance of HIVST with digital innovations, to ease the minds of general users and show them that the result they receive from an HIVST is an accurate representation of their HIV serostatus. Research on this augmentation and interpretation of self-tests with digital supports is a topic is in its infancy.

Chapter II: Manuscript 1 - An Updated Systematic Review of Digital HIV Self-Testing on Outcomes from Accuracy to Linkage (2012-2023)

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Abstract

Background: Human immunodeficiency virus (HIV) self-testing (HIVST) has drastically gained momentum over the past several years following the approval of self-testing methods and novel technological advancements. Digital HIVST is the process of completing an oral- or blood-based HIV self-test with the support of a digital innovation including web-based platforms, social medias, mobile applications, text messaging, and/or digital vending machines (DVMs). We conducted a systematic review on the existing data analyzing digital HIVST accuracy, while updating research on digital HIVST acceptability, preference, feasibility, and impact to show the high records from this self-testing method.

Methods: We searched two databases (Embase and PubMed) for records on HIVST with digital supports. For accuracy measures, the search spanned January 1st, 2013, to May 15th, 2023. For secondary outcomes, the search spanned June 16th, 2021, to May 15th, 2023, updating existing literature from a previous systematic review by McGuire et al., 2021. Quality of studies was assessed using the Newcastle-Ottawa Scale and the Cochrane Risk of Bias Tool 2.

Results: 26 studies were also synthesized as they reported on metrics beyond accuracy, including acceptability, preference, feasibility, and impact outcomes. 80.8% (21/26) of these studies were observational and 19.2% (5/26) were randomized controlled trials (RCTs). Acceptability and preference outcomes drastically ranged from 64.5% to 98.7% (n = 10) and 4.6% to 99.3% (n = 5), respectively. Feasibility included test uptake (42.2%-98.2%; n = 13), response rate (26.0%-94.8%; n = 5), and visits to web-based providers (43.0%-70.7%; n = 2). Impact outcomes assessed new infections (0.1%-10.1%; n = 17), first-time testers (0.0%-45.0%; n = 16), result return (22.1%-97.5%; n = 12), and linkage to care as both connections for

confirmatory testing (60.2%-100.0%; n = 6) and referrals for treatment initiation (44.4%-98.1%; n = 5).

Results from five studies reported on the accuracy of HIV self-tests; all of which were observational studies (5/5). Diagnostic performance metrics, including point estimates of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were measured for oral-based HIVST (n = 1): 92.9%, 96.8%, 76.5%, and 99.2%, respectively. The percentage of invalid test results for oral- and blood-based self-tests ranged from 0.2%-12.7% (n = 4).

The quality of studies varied, though was generally low risk of bias.

Discussion: Digital innovation support was used to improve accuracy of self-tests and resulted in the high accuracy of HIVST results. Innovations were accepted and preferred by participants. Operationally, they were found to be feasible and produced significant impact on the process of HIVST. These findings support digital HIVST as a promising tool to facilitate HIVST, helping to reach UNAIDS targets to end the HIV epidemic.

2.1 Introduction

2.1.1 Background

To meet the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets, human immunodeficiency virus (HIV) self-testing (HIVST) strategies have been deployed in many Southwestern African, North American, European, and Asian countries. HIVST methods have risen in popularity since being approved by the Food and Drug Administration (FDA) in 2012 [1]. HIV self-tests are now offered as oral- or blood-based options that allow users to receive their self-test result within minutes, opposed to waiting days for a laboratory result [1]. Alongside the upsurge in use of HIVST, digital innovations that support HIVST are becoming widely-used in healthcare, adding particular value to this method of self-testing. Digital health innovations are defined by the World Health Organization (WHO) as technologies that assist in the success of health outcomes [2]. The WHO is pushing for adoption and scale-up of digital health innovations in order to improve health developments around the world, in support of its One Health Agenda [3]. HIVST with digital support shows valuable promise in terms of improving outcomes for patients such as linking them to care and detecting new infections [4].

As a result of the increased popularity of self-testing methods, systematic reviews have been conducted to summarize globally collected evidence focused on HIVST systemic outcomes. A prior review by Stevens and colleagues evaluated the accuracy of HIVST, notably without digital supports [5]. However, the review found that groups of participants tended to perform the self-tests well, but there were some exceptions to this, as common mistakes included failing to prepare the kit properly, misconducting sample collection, and spilling the buffer solution [5]. Despite the expansive integration of digital methods with self-testing in recent years, there has

been limited work focusing on the role of digital support complementing HIVST, specifically regarding the performance of said tests.

Performance accuracy of self-tests varies tremendously and depends on the user, type of test, and test setting, such as with or without the assistance of healthcare professionals. A systematic review by Figueroa et al, concluded that HIVST innovations were a reliable and accurate means of testing when conducted by the general population compared to when healthcare practitioners conducted diagnostic tests [6]. These reviews provide insight into the accuracy of HIVST, but to date, there have been no systematic reviews conducted to assess HIVST accuracy evaluated with the support of digital innovations.

As well, our lab has conducted research on support of HIVST over the past two decades. Studies have shown that various populations are highly accepting of HIVST, including rural populations, healthcare workers, young people, and MSM [7, 8, 9, 10]. In one study, we found that 98.8% of MSM participants found the digital component of the self-testing process to be particularly useful [11]. Other work, including a systematic review, also found digital innovations to make a significant impact on HIV healthcare including improvement in ART adherence (pooled OR=2.15 (95% CI: 1.18-3.91)) and clinic attendance rates (pooled OR=1.76 (95% CI: 1.28-2.42)) [12]. These findings suggest that not only can digital supports be embraced and useful as a part of the self-testing process, but also in continuation of care.

However, other outcomes, such as acceptability, preference, feasibility, and impact, have been investigated in conjunction with digital technologies. A systematic review by McGuire et al., published in 2021, evaluated studies from January 1st, 2010, to June 15th, 2021, that focused on patient-reported outcomes including acceptability and preference, and operational feasibility and impact of HIVST methods along with digital innovations [13]. The digital supports of this

review included website-based interventions, social media and app-based innovations, short messaging service (SMS)-based innovations, and digital vending machines (DVMs). This review found that these forms of digital support resulted in reasonably high acceptability (77%-97%), preference (53%-100%), feasibility (93%-95%), and impact (53%-100%) [13]. However, this review also neglected to include accuracy metrics, considering that, at the time, the amount of literature on the accuracy of digital HIVST methods was not sufficient.

Since then, digital innovations have become a rapidly evolving field and COVID-19 has further catalyzed innovations in the self-testing space, facilitating accuracy reporting. Therefore, to address the gaps in evidence regarding the effect of these interventions, we conducted a systematic search from January 1st, 2013, to May 15th, 2023, to update the previous systematic review but with a focus on accuracy as an outcome of interest. 2013 was chosen as the initial search date, considering the Food and Drug Administration (FDA) did not approve the use of oral-based HIV self-tests until 2012 [14]. In addition, to expand upon the work of the previous systematic review with respect to outcomes such as acceptability, preference, feasibility, and impact, we conducted a separate search from June 16th, 2021, to May 15th, 2023, which analyzed these outcomes via digital methods of HIVST [13]. The notion of this review was to generate evidence to guide policy, practice, and research.

2.1.2 Study Objective:

Our objective was to update global evidence on digital HIVST given the recent interest in the field. We aimed to ascertain how digital supports impact systemic patient outcomes, such as the accuracy self-test results. We also set out to update evidence on outcomes with digital innovations for self-tests, including patient-reported and operational outcomes such as acceptability, preference, feasibility, and impact.

2.2 Methods

2.2.1 Search Strategy

A search strategy was developed to extend the work of the past systematic review [13]. We followed the protocol from the prior systematic review, registered on PROSPERO (registration number: CRD42020205025), and modified the strategy to include a new outcome, as described in these methods.

We followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane guidelines to report and conduct the review.

No study participants or members of the public were involved in the design, conduct, or reporting of this review.

2.2.2 Information Sources

Two reviewers (AB, OV) searched two electronic databases (PubMed and Embase), first, for records pertaining to accuracy measures for the period of January 1st, 2013, to May 15th, 2023 (Appendix Search String 1); and second, for new records pertaining to acceptability, preference, feasibility, and impact for the period of June 16th, 2021, to May 15th, 2023 (Appendix Search String 2). Notably, there was an overlap of three papers that qualified for both the accuracy and secondary outcome searches [15, 16, 17]. We retrieved all full text studies and conference abstracts, with both authors (AB, OV) independently screening publications in both searches. No restrictions were placed on language in either search.

2.2.3 Eligibility Criteria

We included all studies (observational and interventional) evaluating digital innovations facilitating HIVST in any country and those reporting quantitative results. We included studies

only if the digital supports were significantly used in the HIVST process (administration, education, communication, result interpretation, etc.).

We excluded qualitative studies, reviews, protocols, modelling studies, commentaries, narrative studies, case reports, and editorials; studies that did not have HIV as their primary focus, did not include HIVST, or did not employ a digital technology; as well as studies not written in English.

2.2.4 Study Selection and Data Abstraction

Titles, abstracts, and full texts were screened independently by two reviewers (AB, OV) for eligibility, and the final included data were independently abstracted. Abstracted data included: study design, country, sample size, study population characteristics, digital innovation type, intervention description, and key findings. A senior reviewer (NPP) was consulted for resolution of disagreements. We abstracted data from a total of 28 publications.

2.2.5 Summary Outcome Measures and Narrative Synthesis of Results

We found significant heterogeneity in reporting of interventions, study designs, and outcome metrics (reported variously) that precluded a meta-analysis.

To evaluate the integration of digital technology in HIVST, the primary outcome explored was accuracy, and the secondary outcomes explored were acceptability, preference, feasibility, and impact. Accuracy was assessed through metrics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), which are defined in Table 1 [18]. The reference as to what these metrics were referring to vary throughout the studies but is generally a comparison of the self-test to the gold standard which consists of dual rapid tests

and/or HIV RNA test, along with a laboratory test result. As well, secondary outcomes were adapted from the previous systematic review and are defined in Table 2 [13].

Table 1: Accuracy metrics definitions

Metric	Definition
Sensitivity	A test's ability to correctly identify those with the disease – the proportion of true positive (numerator) over the proportion of true positives and false negatives (denominator).
Specificity	A test's ability to correctly identify those without the disease – the proportion of true negatives (numerator) over the proportion of true negatives and false positives (denominator).
Positive Predictive Value	The probability that the disease is present, given the test result is positive – the number of true positives (numerator) over the number of true positives and false positives (denominator).
Negative Predictive Value	The probability that the disease is absent, given the test result is negative – the number of true negatives (numerator) over the number of true negatives and false negatives (denominator).

Table 2: Outcome measures and definitions

Outcome	Definition
Acceptability	The ease of use and willingness of participants to use digital innovations for HIVST, defined as those who agreed to use/try the digital innovation (numerator), over all those who were enrolled in the study (denominator).
Preference	The proportion of study participants who preferred HIVST with digital supports over conventional HIV testing, defined as those who prefer this method of self-testing (numerator) over all those who were enrolled (denominator).
Feasibility	The convenience of using HIVST with digital supports – reported with self-test uptake, response rate, and visits to web-based HIVST providers.
Impact	A statistically significant improvement in measured outcomes compared with a comparator group, or a net change in outcomes amongst a particular group that can be attributed to specific intervention – reported metrics include proportion of

	first-time testers, detection of new infections, HIVST kit return rate, proportion of participants linked to continuative care including counselling and/or confirmatory testing, and proportion of those referred to treatment.

2.2.6 Quality Assessment

The Cochrane Risk of Bias Tool 2 (RoB 2) was used to assess the quality and potential risk of bias of randomized controlled trials (RCTs), and the Newcastle-Ottawa Scale (NOS) was used for cohort and cross-sectional studies [19, 20].

2.2.7 Role of Funding Source

NPP acknowledges support from the Fonds de recherche du Québec – Santé (Distinguished Research Scholar Award, 324154). The agency had no role in the writing of the manuscript or the decision to submit it for publication.

2.3 Results

2.3.1 Study Selection

Accuracy

63 records were retrieved during our accuracy search and two were identified from our secondary outcomes search, presenting accuracy outcomes. Overall, five of these records were included in the final analysis (Figure 1).

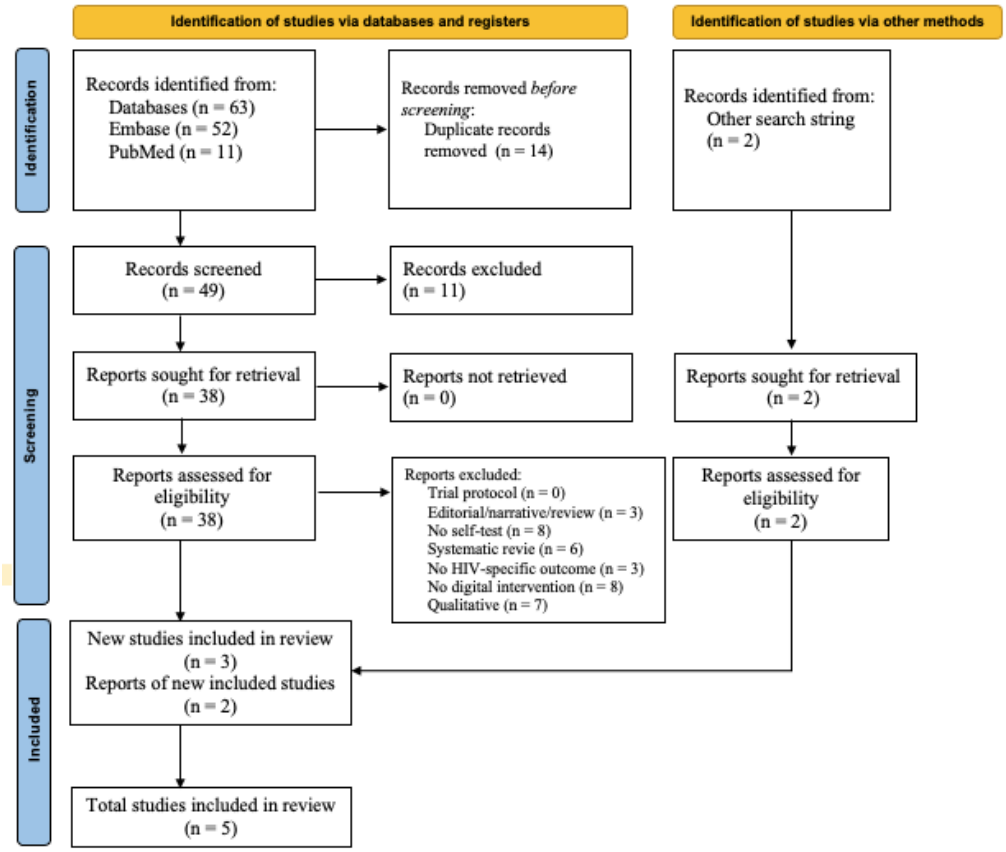

Figure 1: Study selection of accuracy search

Secondary Outcomes

Of 209 records retrieved through this search, 24 studies were included, along with two studies from the accuracy search, for a total of 26 studies in the final analysis of secondary outcomes (Figure 2).

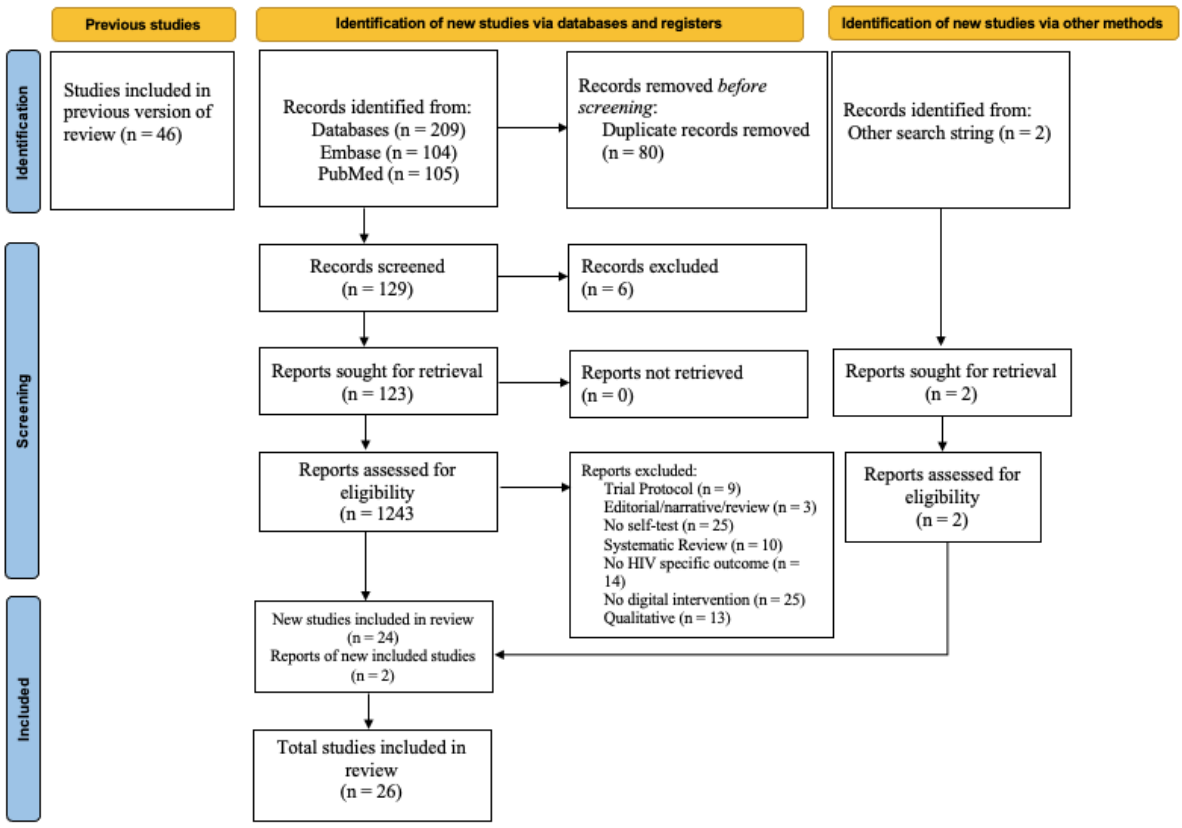

Figure 2: Study selection of secondary outcomes search

2.3.2 Study Characteristics

Accuracy

The five papers that were included for exploration of accuracy included one study from each of the following countries: Canada, United Kingdom (UK), and United States (US); as well as two studies from China. Of the five studies, three were cross-sectional (60.0%), while two were cohort studies (40.0%).

Two (40.0%) of the studies analyzed the general population, and the other three studies (60.0%) recruited key populations such as men who have sex with men (MSM), or specifically Black, African American, or Latinx MSM. Their sample sizes ranged from 271 to 3259, with a

median of 442 participants. Further details of the study characteristics can be found in Appendix Table 1.

The digital supports that were analyzed in the accuracy studies were primarily website-based HIVST innovations (80.0%, 4/5), but one study looked at a multi-modal approach to HIVST including app-based, SMS-based, social media, and web-based innovations.

Secondary Outcomes

26 studies reported on secondary outcomes from ten countries. Studies were primarily recorded in China (23.1%, 6/26) and South Africa (23.1%, 6/26), followed by the US (19.2%, 5/26), Canada (11.5%, 3/26), and 3.8% (1/26) in each of the following countries: Australia, Brazil, Japan, India, Philippines, and Thailand. Sample size varied from 120 to 9505, with a median of 1083 participants (Appendix Table 2. In terms of study designs, 80.8% (21/26) of studies were observational, with 65.4% (17/26) being cross-sectional, and 15.4% (4/26) being cohort studies. There were several RCTs found in the review, with 19.2% (5/26) of the studies following this design.

Most studies focused on vulnerable populations, with 69.2% (18/26) focusing on MSM populations, 19.2% specifically focusing on Black, African American, or Latinx MSM (5/26), and 7.7% (2/26) assessing transgender women. About one third (34.6%, 9/26) of studies were evaluated in the general population.

Over half (61.5%, 16/26) of these studies evaluated outcomes from web-based innovations. Social media and app-based innovations were the second most popular type of innovation with 30.8% (8/26) of studies reporting these technologies. Digital vending machines

(DVMs) were reported in one study, and about 15.4% (4/26) of studies reported using multi-modal approaches including web-based, social media, and/or SMS-based interventions.

2.3.3 Risk of Bias in Studies

Cochrane Risk of Bias Tool 2 (RoB 2)

Using the RoB 2 tool, we found low risk of bias for the included RCTs (Figure 3). Blinding of participants was only possible before the trial and was reported by 60.0% (3/5) of studies. Although blinding of the participants and assessors through the trial and analysis was not possible, due to the assessed outcomes of digital supports, there were no deviations from the intended interventions that arose in any of the studies. As well, every study had majority or all of the data present in the analysis, limiting selection bias. Finally, the outcome results were all measured as efficiently as possible, given the metrics of the studies, therefore limiting reporting bias as well.

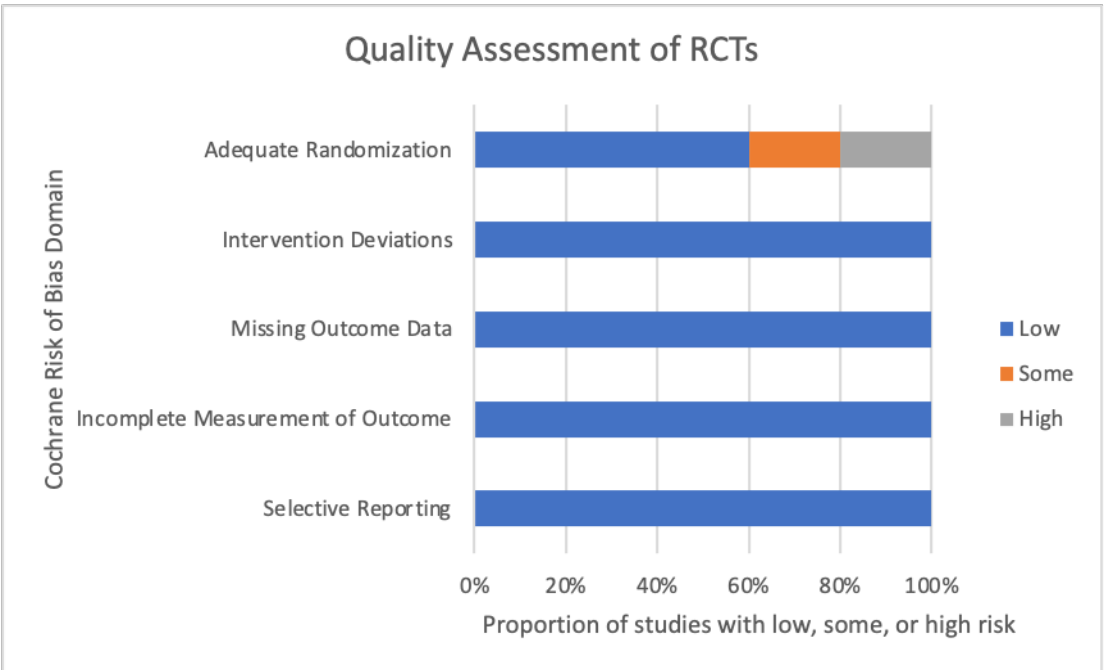

Figure 3: Risk of bias assessment of RCTs using the Cochrane Risk of Bias Tool 2

Newcastle-Ottawa Scale (NOS)

Using the NOS, we found observational studies overall ranged from low risk to some risk (Figure 4). Possibility of selection bias, confounding, or outcome/exposure misclassification was found in 19.0% (4/21), 9.5% (2/21), and 9.5% (2/21) of these studies, respectively. Of the cohort studies, 75.0% (3/4) had risk of attrition bias. Many cross-sectional studies (82.3%, 14/17) had unjustified sample sizes, but 70.6% (12/17) studies had sufficient sample sizes ranging from 692 to 9505.

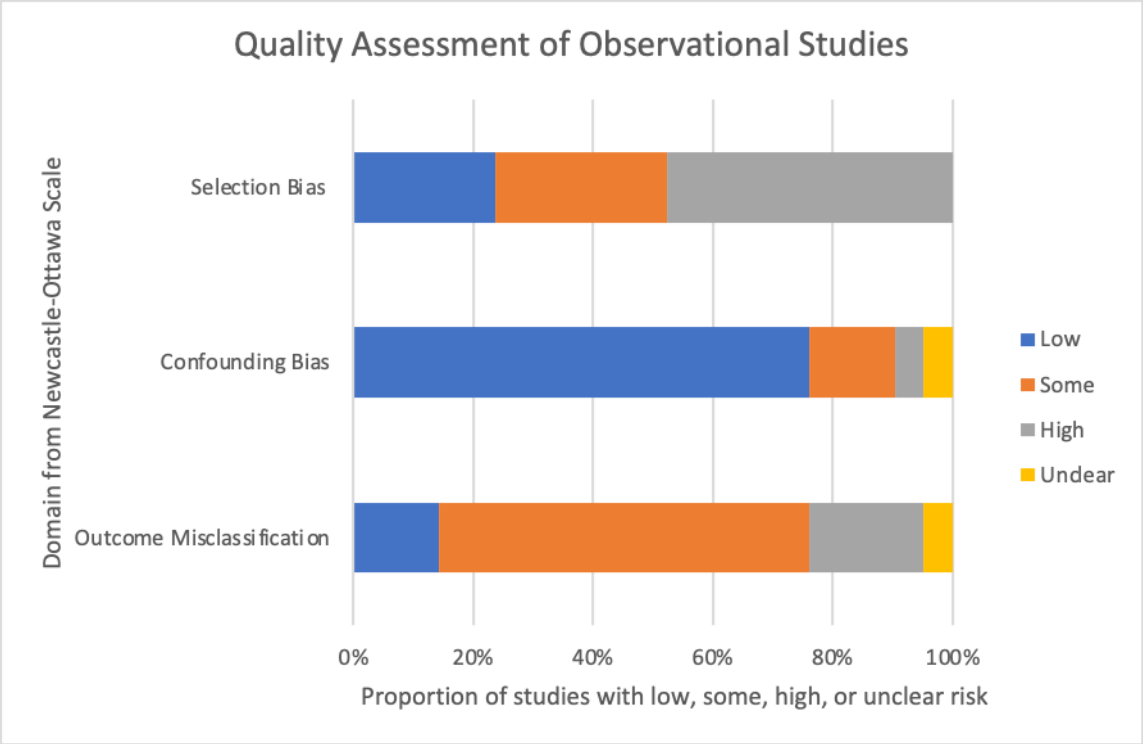

Figure 4: Risk of bias assessment of observational studies using the Newcastle-Ottawa Scale

2.3.4 Accuracy

Five studies evaluated the accuracy of HIVST integrated with the use of digital innovations [15, 16, 17, 21, 22]. 40.0% (2/5) of these papers reported accuracy of blood-based

self-tests [17, 21]; whereas 40.0% (2/5) reported accuracy of oral-based self-tests [15, 22]. The remaining study allowed participants to choose between oral- or blood-based self-tests but reported no differences in accuracy between the two types of tests [16].

80.0% (4/5) of these studies reported accuracy as the percentage of invalid test results, which ranged from <0.2% to 12.7% [15, 16, 17, 21]. Though none of the studies explicitly define invalid test results, these are generally measured as test results that did not correspond to the expected outcome of control and test lines for either negative or positive results.

Wang et al. reported accuracy of the oral-based Aware™ HIVST as sensitivity, specificity, PPV, and NPV, but notably only as point estimates and not with confidence intervals [22]. These were reported as 92.9% (13/14), 96.8% (121/125), 76.5% (13/17), and 99.2% (121/122), respectively [22]. In this study, the participants were asked to conduct the self-test onsite and reported their result to the researcher as soon as it was available.

Kwan et al. allowed participants to choose between an oral- or blood-based HIVST but did not include mention the manufacturers of this tests in the publication, which can impact accuracy measurements [16]. The study reported that two of the four positive HIV self-tests were confirmed to be positive, but neglected to mention if these results were from the oral- or blood-based self-testing options. The participants of this study ordered the self-test and completed it at home, then uploaded their self-test result onto the web-based platform, which could have contributed to the few positive self-tests received. This study also reported the agreement of test interpretation between participants and the research team as 99.1% (95% CI: 97.4%-99.8%).

Brady et al. reported that of the total 24,717 blood-based self-test kits purchased during the study, only three presented participants with false positives, which was much lower than the number they had expected [21].

Further details regarding these key findings can be found in Appendix Table 3.

2.3.5 Secondary Outcomes

Outcome measures beyond accuracy become important when real life implementation is called into question. Due to this, we explored patient-reported acceptability and preference, and operational feasibility and impact outcomes. Further details regarding these key findings can be found in Appendix Table 4.

Acceptability

38.5% of the studies (10/26) reported acceptability measures [23-32]. 50.0% (5/10) of these studies analyzed the willingness of participants to use the self-test with the digital intervention and was consistently found to be high, ranging from 72.2% to 99.0% [25-28, 32]. The study by Rosadino et al. was a quasi-RCT that demonstrated the willingness of participants to use a community-based HIVST distribution model [32]. This study found that 99.0% (4163/4205) of respondents were interested in getting an HIV self-test [32].

The five remaining studies (50.0%, 5/10) reported acceptability as the ease of use of the digital interventions, although reports defined the ease of use in various manners [24, 25, 29-31]. Two studies showed that 64.5% and 73.5% of respondents found the digital innovation easy or very easy to use [30, 31]. One of these studies was an RCT that evaluated acceptability measures of an infographic for HIVST, finding that 73.5% of those who interacted with the intervention agreed that it was easy to use [31]. Another study reported that only 7.5% (9/120) of participants

said the digital support was easy to use, but they quoted that participants said, "*It is very easy to use, less stressful very understandable, it is the best and very advanced product one could ever wish for."* [29]. Alternatively, one study reported ease of use using a Likert scale and found a score of 3.8 (SD=1.6) for the ease of uploading results, and a score of 4.2 (SD=0.9) for ease of finding a clinic using the digital innovation [25]. The remaining paper reported ease of use by assessing whether participants thought the innovation was helpful [24]. A majority of participants agreed that it was helpful for the following matters: understanding their current risk (85.6%), testing results (97.6%), concept of window period (88.8%), reducing fear towards HIV testing (72.0%), and reducing high-risk behaviours (80.0%) [24].

Preference

Preference was assessed in 19.2% (5/26) of the studies [16, 26, 29, 33, 34]. Preference for the digital innovation compared to standard testing methods was reported in three of the papers and ranged from 63.0% to 99.3% [26, 29, 34].

One study analyzed data from 794 participants who ordered HIVST online, and noted their reasoning for preference of HIVST online versus other methods of testing was due to convenience (79.0%), not wanting to wait for results (44.0%), not wanting to talk about sex with anyone (33.0%), not having time to go elsewhere for testing (29.0%), and fear of stigma (22.0%) [33]. Notably, 21.0% (40/190) of participants who responded to the survey question said they would not test elsewhere at all [33].

The final study had lower rates of preference; the majority of participants who requested a self-test did not want any form of support (77.9%) [16]. However, of those who did want support, digital forms of support including instant messaging, video calls, and chatbots were

preferred by 65.8% (102/155) of respondents, compared to in-person support (47.7%, 74/155) [16].

Feasibility

Feasibility was assessed in 61.5% (16/26) of the studies [15-17, 23-25, 30, 32, 33, 35-37, 40-43]. 81.2% (13/16) of these studies reported uptake of self-tests [15-17, 24, 32, 33, 35, 36, 37, 40-43]. Eight of these papers reported uptake as percentages, ranging from 68.3% to 98.2% [15, 16, 24, 32, 35, 37, 40, 41]. Two of the remaining studies reported uptake as the number of HIVST kits ordered throughout the study – one reported that 701 kits were ordered by 604 participants, and the other reported that 834 tests were ordered by 309 participants [17, 43]. The study by Bell et al. reported that of the 794 participants who ordered an HIVST, 95 of them ordered multiple self-testing kits, ranging from two to seven kits ordered per person [33].

An RCT conducted in the United States investigated the effect that a peer-led online community had on the uptake of the blood-based myLAB Box HIVST. This study found there was an increase of 6.2% in test uptake between the intervention and control groups [42]. Another RCT conducted in China analyzed the effect of monetary incentives and online peer-referrals on test uptake of the blood-based SD BIOLINE HIV/syphilis self-test [43]. This study found that the 102 control participants ordered 222 kits, the 103 participants of the monetary intervention group ordered 275 kits, and the 104 participants in the monetary and peer-referral intervention group ordered 337 [43].

19.2% (5/26) of studies reported the response proportion of participants and found results ranging from 26.0% to 94.8% with an outlier, but ranging from 61.1 to 94.8% without the outlier [16, 33, 39, 42, 43]. The outlying response frequency of 26.0% found in one study was referring

to responses of the optional online survey asking questions on the quality of their experience, that participants were offered once the self-testing process was complete [30].

In an RCT by Young et al. the response proportion was higher among the intervention group (93.4%, 421/450) compared to the control group (92.9%, 418/450) [42]. As well, the RCT by Zhou et al. found the response rate to be higher among the intervention groups (94.2% and 96.2%) compared to the control group (94.1%) [43].

Feasibility was reported as visits to the web-based provider in two studies, with rates of 43.0% (1475/3431) and 70.7% (531/751) [23, 25].

Impact

Impact was measured in 92.3% (24/26) of the studies [4, 15-17, 23-28, 30, 32-41, 43-45]. [4, 9, 10, 11, 17, 18, 19, 20, 21, 22, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, 38, 39].

Impact reported as the detection of new HIV infections was the most prominent metric used in 73.9% (17/23) of the studies. [4, 15, 16, 24-26, 32, 33, 35, 36-41, 43, 44]. A majority of these papers (64.7%, 11/17) reported the proportion of new infections by HIVST which varied from 0.2% to 9.8% [15, 16, 25, 26, 32, 37-41, 44]. One of these 11 studies noted that 41.1% (130/314) of the participants that tested positive had not received a positive result before [39]. The other six papers reported the proportion of new infections as those that were confirmed by laboratory testing and these ranged from 0.1% to 10.1% [4, 24, 33, 35, 36, 43]. The quasi-RCT by Pai et al. found the proportion of new infections to be higher among the intervention groups (8.9%), which included unsupervised and supervised self-testing, compared to the control group (6.8%) which only received laboratory gold standard testing and not HIVST (RR: 1.304, 95% CI: 1.023-1.665) [4].

The proportion of "first-time testers" were reported in 16/23 studies (69.6%) [16, 17, 23, 26-28, 32-35, 37, 38, 40, 41, 43, 44]. The proportion of first-time testers for 14 of these studies ranged from 14.5% to 45.0% [16, 17, 23, 26-28, 32-35, 37, 40, 43, 44]. Additionally, one study looked at those tested positive, and found that all of them were first-time testers [41]. Another study looked at the difference in rate of first-time testers among White participants compared to African, Caribbean, and Black (ACB) participants and found that the proportion of White first-time testers was 21.0%, compared to 30.0% among ACB participants [38].

Return proportion was defined as the percentage of reported results from participants. 52.2% (12/23) of the studies reported this metric, ranging from 22.4% to 97.5% [15, 17, 25, 32, 37-41, 43-45]. An RCT by Zhou et al. found that the return rate among the control group (94.0%) was higher than the intervention group that did not receive online peer-referral (93.4%), but was lower than the intervention group that did receive online peer-referral (97.3%) [43].

Linkage to care was observed in 47.8% (11/23) of studies [4, 24, 26, 30, 32, 33, 35, 36, 40, 41, 44]. 54.5% (6/11) of these studies reported this metric as confirmatory HIV testing and linkage to treatment, which varied from 60.2%-100.0%. [24, 26, 30, 32, 33, 35]. The remaining five papers (45.5%) reported linkage to care as the percent of confirmed HIV-positive participants who were referred to and initiated anti-retroviral therapy (ART) and ranged from 44.4% to 98.1% [4, 36, 40, 41, 44].

The quasi-RCT by Pai et al. found high linkage to care among all study arms, with a greater proportion for the intervention groups (99.8%) compared to the control group (98.5%) (RR: 1.012, 95% CI: 1.005-1.018). As well, 98.1% of all those who were HIV-positive were referred to start ART [4]. This study also showed that 16.7% of participants in the self-testing

arm referred someone in their social network, whereas only 3.1% of participants in the conventional testing arm did so (RR: 5.435, 95% CI: 4.024-7.340) [4].

2.4 Discussion

2.4.1 Key Findings

Accuracy

Accuracy, assessed as sensitivity, specificity, PPV, and NPV, is a key indicator of diagnostic performance. It is notable that past studies have shown the accuracy of blood-based tests, in terms of sensitivity, is slightly higher than oral-based tests [46]. However, majority of the accuracy papers solely reported on invalid rates so a direct comparison between the self-testing types was not inferable.

Invalid tests were not explicitly defined in any of the studies but were assumed to be referring to a result that was neither negative nor positive. Invalid results are a product of the test itself being defective, the user conducting the test incorrectly, or the result simply being misinterpreted. Although this metric is not one of the key assessors of accuracy, it is an important aspect to consider for diagnostic performance, considering when a user receives an invalid test result, their trust in the self-testing process may diminish. The WHO and other governing bodies do not have a range or any percentage of invalid tests that are acceptable for screening tests. So, what is an appropriate amount without causing distress of a test's ability to perform? As well, are these invalid results more of an indication that the tests are defective or that they are not performed properly by users? Interestingly, by far the highest percentage of invalid test results, 12.7%, was conducted in Canada, using the blood-based bioLytical INSTI® self-test which is the only HIVST approved in the country [17]. Is this an appropriate percentage

to allow for federally approved self-tests? Research should be conducted to answer these questions, as well as define an acceptable percentage range of invalid tests at the level of approval.

It is worth noting that while the proportion of invalid tests is a relevant metric, it is key to also report other related metrics that help in estimation of the overall diagnostic performance. Accuracy metrics such as sensitivity, specificity, PPV, and NPV are crucial for evaluating the performance of HIVST, determining the reliability of results, and to assist in pooling outcomes for meta-analyses.

Although there were five studies reporting high diagnostic performance with HIVST as low proportion of invalid tests or high sensitivity, specificity, PPV, and NPV, the overall body of literature in this area remains sparse. No studies assessed the improved accuracy of HIV self-testing with digital interventions compared to without digital interventions. This highlights the need for further research to explore the potential of digital innovations in improving the accuracy of HIVST.

Furthermore, it is important to highlight that the one study reporting all the ideal accuracy measures evaluated the impact of internet use on HIVST uptake and performance, rather than specifically assessing the impact of digital innovations on the self-testing process itself [22]. This indicates a research gap in understanding the direct influence of digital interventions on the accuracy of HIVST. This study also reported mediocre percentages of accuracy, which indicates there is room for improvement if digital supports are implemented during the testing process specifically.

Acceptability

The acceptability of digital interventions in the context of HIVST varied across the studies included in this systematic review. Different studies reported differing levels of acceptability among participants, indicating that acceptability is influenced by various factors. Willingness to use digital interventions was consistently reported as high across the studies, with rates ranging between 72.2% to 99.0%. This suggests that individuals are generally open and receptive to incorporating digital technologies into the self-testing process.

Reports on the ease of use of digital interventions showed some variability among the studies. However, it is important to note that the results may have been influenced by the survey response rate, as participants who found the digital interventions challenging or problematic might have been more likely to provide feedback. It is also worth mentioning that some of the studies included in this systematic review did not specifically use the digital intervention for performing the self-test itself, but rather was used to ask participants their likelihood of using an HIV self-test.

To improve the acceptability of digital interventions, future developments should consider catering to the entire HIVST process, including sample collection and result interpretation. By integrating digital technologies at every step of the process, including user-friendly interfaces and clear instructions, the overall acceptability of digital interventions can be enhanced.

Preference

The findings of this systematic review indicate generally high rates of preference for digital interventions in the context of HIVST, ranging from 63.0% to 99.3% across the included

studies. This suggests that a significant proportion of participants favored the use of digital innovation in the HIVST process.

Only one study from China reported lower rates of preference for any form of support during the HIVST process, as most participants in that study expressed a preference for not receiving any support [16]. However, among those who did desire support, digital options were preferred over in-person support. This highlights the individual variability in preferences and the importance of tailoring interventions to meet the diverse needs and preferences of users. The novelty of digital innovations can be overwhelming, particularly among older generations and individuals who are less familiar with technology, which may influence their preferences of digital interventions for HIVST. It is crucial to consider the target population and their digital literacy level, and to provide adequate support, education, and user-friendly interfaces to address potential barriers related to technology adoption.

Feasibility

The high uptake of self-tests facilitated by digital interventions suggests the accessibility and convenience associated with digital HIVST. This indicates that digital interventions can play a crucial role in promoting the uptake of HIVST, making testing more accessible to a broader population.

In the RCT conducted by Young et al., the overall uptake of HIVST was relatively low, but the inclusion of a digital component resulted in increased test uptake by 6% with an odds ratio of 1.43 (95% CI: 1.04-1.95). This highlights the potential of digital interventions to positively influence self-test uptake rates [42].

The study by Mshweshwe-Pakela et al. reported a significant 25.0% increase in clinical HIV testing through the implementation of a digital solution [36]. This finding has important implications, suggesting that the widespread application of digital innovations in HIVST could contribute significantly to achieving the UNAIDS 2025 targets of increased HIV serostatus knowledge and treatment.

There was substantial variation in response rates across the studies, which may have been influenced by the differences in follow-up procedures and the fact that different populations were recruited in different countries. It is important to track and analyze response rates to assess the performance of digital interventions and identify effective methods for obtaining feedback via digital means.

The feasibility of visits to web-based providers also varied across the studies, which can be attributed to differences in the methods of exposure to digital innovations. For example, in the study by Birdthistle et al., the intervention involved a campaign about HIVST disseminated through social media platforms [23]. Considering social media applications use algorithms that influence who is exposed to what type of advertisements, it is possible that this played a role in determining the exposure of individuals to the digital intervention.

Altogether, the inclusion of digital components has been shown to increase test uptake, and the feasibility of digital interventions are supported by the available evidence. However, response rates and variations in exposure methods should be carefully examined and addressed to optimize the performance and impact of digital interventions in HIVST.

Impact

The use of HIVST methods with digital support has shown potential in reaching the first of the UNAIDS 95-95-95 targets and is supported by the proportions of new infections and first-time testers in this review.

There was a limited difference in ranges of new infections identified via HIVST compared to confirmed HIV cases, 0.2%-9.8% versus 0.1% to 10.1%. The similarity between these rates indicates that HIVST with digital support is a valuable tool for identifying new cases of HIV. Importantly, the study conducted by Pai et al. showed a 2.21% (RR: 1.305, 95% CI: 1.023-1.665) increase in the proportion of new infections among the HIVST arm compared to the conventional testing arm, which is supporting evidence of digital supports increasing HIV detections and bringing us closer to the first UNAIDS target [4].

The proportion of first-time testers supports the notion that digital innovations enhance easy access to HIVST. If digital means of HIVST are made more accessible to the general population, it is likely that the rate of first-time testers would increase based on the evidence of the included articles. This highlights the potential of digital supports to attract individuals who have not previously tested for HIV, thus expanding testing coverage and reaching those who may not have engaged in traditional testing methods.

In the study led by our lab, the unsupervised versus supervised comparisons reflected the popularity of unsupervised self-testing [4]. This finding is relevant because a bulk of the general population will have greater access to self-tests with digital supports in the near future and the increased uptake by first-time testers gives confidence to support the scale up of these innovations.

The return rates of test results were high among majority of the studies and can likely be attributed to the accessibility and convenience provided by using digital supports to report test results. The ease of reporting results digitally eliminates the need for individuals to physically visit a testing center or clinic, making it more convenient and potentially encouraging higher rates of result reporting. The low self-test return rate mentioned in the paper by Fischer et al. is an outlier, but was justified by the researchers due to mobile applications losing 80% of their users after one week [25]. Notably, this study was conducted in South Africa in 2018/2019, so there is a possibility that if the same study was conducted today, there would be very different results, given the utilization of mobile apps and self-testing methods used through the COVID-19 pandemic.

Linkage to care is a critical aspect of HIV testing. HIVST without digital supports have struggled with adequate linkage to care [48]. Digital innovations contribute greatly to this process, as patients can be directly connected to care without having to navigate the resources themselves. In one study, there was linkage to post-test counsellors, who facilitated staging the disease of those who tested positive, and assisted in preventative practices for those who tested negative, leading to a 99.7% linkage proportion among the self-testing arm [4]. The findings of this systematic review support this assumption as the high proportion of individuals who received a positive self-test result were connected to confirmatory testing, which indicates that the accessibility provided by digital support likely facilitates follow-up testing in real-world settings.

Furthermore, there was a high proportion of individuals who were confirmed to be HIV-positive and started ART treatment which demonstrates the promising potential of digital interventions in successfully connecting HIV-positive patients to continuative care. These

findings highlight the practicality and convenience of digital interventions in the HIV testing and care continuum.

However, it is notable that the linkage to treatment initiation was primarily found to be high in studies that were conducted in South Africa (80%-98.1%), China (97.1%), and India (87.5%) compared to the low proportion of treatment initiation found in the US (44.4%) [4, 36, 40, 41, 44]. The explanations for this low linkage to care proportion in North America compared to middle-income countries should be further explored. However, one possible explanation for this drastic difference could be the variation in healthcare systems.

The bulk of the population in the United States (68.4%) are insured by a private healthcare system [48]. 39.3% of the population are covered by federal programs that are designed to insure those who are 65+ years old, permanently disabled, or belong to a diverse low-income population [48]. Military healthcare services insure 4.9% of the population, which leaves 8.6% of the United States population uninsured, equating to approximately 28 million people [48]. Those left uninsured have very limited public healthcare options and therefore the linkage to care may not be feasibility for some of the US population. It is important to consider insurance coverage and costs of treatments when connecting HIV-positive individuals to treatment options, which is possible to implement via digital support.

Overall, the use of digital innovations in HIVST has resulted in the identification of new infections of HIV, an increased proportion of first-time testers, and a high return rate of test results, as observed in the studies from this review.

Quality Assessment

The RCTs included in this review had a low risk of bias. There is confidence that these studies were well conducted and have trustworthy results.

The observational studies had low risk of confounding bias, but some to high risk of selection bias and outcome misclassification. The high risk of selection bias was mostly due to lack of justified sample sizes. As for outcome misclassification, assessment of the outcome was consistently self-reported, considering the nature of self-testing, thus increasing the risk of bias.

2.4.2 Limitations of Evidence

The findings of this systematic review should be interpreted in light of several limitations related to the available evidence.

First, the heterogeneity of interventions, outcomes, populations, and settings among the included studies precluded the performance of a meta-analysis. This heterogeneity introduces variability and makes it challenging to draw definitive conclusions or generalize the findings across different contexts.

Another limitation stems from the inconsistent terminologies used across the studies. The lack of standardized terminology hampers the synthesis and comparison of results, potentially leading to confusion or misinterpretation of findings. Future research should strive for a common language to enhance clarity and comparability in this field.

Furthermore, the heterogeneity in reporting outcomes poses a challenge in synthesizing the evidence. Variation in outcome measures and their assessment methods makes it difficult to pool the data and establish a comprehensive understanding of the effectiveness of digital supports. Future studies should adopt standardized outcome measures and reporting guidelines to facilitate meaningful comparisons and meta-analyses.

An additional limitation is the limited evidence from low-income countries (LICs). Many studies included in this review were conducted in middle- or high-income settings, such as China, United States, Canada, and South Africa, which may limit the generalizability of the findings to LICs. This highlights the need for more research in diverse geographic and socioeconomic contexts to assess the feasibility and effectiveness of digital health interventions across different resource settings.

2.4.3 Limitations of Review Process

A few limitations in the review process should be acknowledged. First, the search strategy was restricted to two databases, which may have resulted in the potential omission of relevant studies published in other databases. Although efforts were made to ensure a comprehensive search, the possibility of missing relevant studies cannot be completely ruled out.

Moreover, as this systematic review focused on a majority of observational studies, there is a risk of bias. Observational studies inherently lack the randomization and control provided by RCTs, which could influence the observed effects of digital health interventions.

2.4.5 Implications of Results for Practice and Policy

The findings of this review have important implications for practice and policy in the field of digital health interventions.

First, the inclusion of five RCTs (including two quasi-experimental trials), 17 cross-sectional, and six cohort studies in this review provide a comprehensive overview of the existing evidence. These studies offer valuable insights into the effectiveness and potential benefits of digital innovation in healthcare practices in terms of its accuracy, acceptability, feasibility, impact, and preference. Specifically, the presence of several RCTs limited the risk of bias

associated with selection, as participants could be randomly allocated to the control or intervention group in most studies.

In the context of HIVST and digital support, the results of this review highlight several potential benefits. First, digital interventions have shown promise in increasing testing rates and serostatus awareness among individuals. This has significant implications for HIV prevention and control efforts. Additionally, the use of digital platforms for HIVST may offer increased privacy and confidentiality, as well as reduce barriers associated with fear of stigma and judgment. Furthermore, digital interventions allow for efficient data collection, enabling real-time monitoring and evaluation of HIV testing programs that can be applied to future research, while also facilitating linkage to care, which is a key metric to report on advancement towards the UNAIDS targets.

Understanding the benefits and limitations of digital health interventions can inform the development of global guidelines and protocols for their integration into healthcare systems. Policymakers and healthcare providers can leverage these findings to optimize the use of digital interventions which will in turn improve patient outcomes and advance public health goals.

2.4.6 Implications of Results for Future Research

Future studies should focus on examining the specific effects of digital methods on HIVST accuracy to provide a clearer understanding of their potential benefits in improving self-test interpretation. None of the papers included in this review specifically compared the accuracy performance of HIVST with digital interventions to HIVST without digital interventions. This comparison is essential to determine whether digital methods truly assist in improving the accuracy of self-testing. Future research should prioritize such comparative studies to confirm

the role of digital innovations in enhancing the accuracy of HIVST. The limited number of studies assessing the accuracy of HIVST with digital interventions underscores the need for further research in this area.

It is also important to note that majority of the studies in this review were conducted in middle-income countries, therefore highlighting a need for research to be conducted in low-income countries. Research has shown that socioeconomic factors play a significant role in HIV infection rates, which should be considered for studies conducted in low-income countries, where social determinants of health are likely to have more of a negative impact on populations [12, 49]. The freedom of choice that is provided by digital HIVST could be a means by which these negative impacts by sociodemographics can be minimized. As shown by our trial conducted in South Africa, participants were free to choose an unsupervised or supervised HIVST option, and older populations were more likely to choose the supervised option [4]. This was likely due to their limited knowledge of, comfortability with, or access to digital support; but the opportunity to conduct testing in a clinic with assistance nearby made up for their hesitation and provided them with the digital supplies to conduct the self-test [4]. This is necessary to consider in research of low-income countries since only 34% of people in these countries have access to smart devices, so supervised digital HIVST at clinics may be the most effective method of delivering care [50].

Additionally, it is important to consider patient preferences in testing processes, considering this can have a profound impact on retention rates. Qualitative research conducted by our lab has found that users are very appreciative of the flexibility and support that is provided by digital strategies [51]. As well, we have found that patients enjoy conducting tests themselves and being the only person who views the result, in order to maintain privacy and the

sense of security in knowing that the test result is their own [52]. Qualitative work has also found that self-testing makes patients feel safe, comfortable, and less afraid considering there is no need to go to a clinic and converse with another person [53]. These findings all need to be considered in future research in order to develop the most ideal self-testing methods.

The findings of this review highlight the potential of digital innovations to increase accuracy rates, but more robust studies are required. Addressing these gaps will contribute to a more comprehensive understanding of the benefits and limitations of digital innovations in enhancing the accuracy of HIVST.

2.5 Conclusion

Digital supports have demonstrated their ability to enhance HIVST across various domains. They demonstrated successes in high test accuracy, or accuracy of self-test interpretation, followed by desirable metrics of acceptability, preference, feasibility, and most importantly impact.

First, digital interventions have the potential to improve test accuracy by providing clear instructions, result interpretation, and data collection mechanisms. By integrating digital technologies into the HIVST process, the accuracy rates of self-tests can be increased, promoting reliable and trustworthy results; however, more evidence is needed in this space. Second, digital interventions have shown positive effects on acceptability. The convenience and privacy associated with digital means contribute to higher acceptability rates among individuals. Third, digital interventions are preferred by a significant proportion of individuals, for their convenience, privacy, and empowerment. This preference indicates the potential for digital interventions to become an integral part of healthcare, particularly in a field as stigmatized as

HIV testing and treatment, where people may be hesitant to seek traditional options. Furthermore, digital support enhances the feasibility of HIVST. By leveraging technology, digital means provide easy access to testing and result reporting. This accessibility eliminates the need for physical visits to testing centres or clinics, making testing more feasible for individuals with time constraints, limited mobility, or those residing in remote areas. Finally, digital innovations also have a significant impact on HIVST as they contribute to increased result returns, reach first-time testers, identify new infections of HIV, and improve the proportion of patients linked to care. By leveraging the widespread use of technology, digital interventions can extend the reach of HIVST and bridge gaps in testing coverage.

Considering the technological advances taking place in our world, the integration of digital interventions into healthcare, including HIVST, is a logical step forward. The use of digital innovations aligns with the evolving healthcare landscape and has the potential to revolutionize HIV testing, ultimately leading to better health outcomes for individuals and communities.

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2.7 Appendix

Search String 1: *((hiv[Text Word] OR human immunodeficiency virus[Text Word]) AND (self-test[Text Word] OR self test[Text Word] OR self-testing[Text Word] OR self testing[Text Word] OR self-sample[Text Word] OR self sample[Text Word] OR self-sampling[Text Word] OR self sampling[Text Word]) AND (digital[Text Word] OR Mhealth[Text Word] OR mobile health[Text Word] OR online[Text Word] OR web-based[Text Word] OR website[Text Word]) AND (accuracy[Text Word] OR accurate[Text Word] OR validity[Text Word] OR valid[Text Word] OR sensitivity[Text Word] OR sensitive[Text Word] OR specificity[Text Word] OR specific[Text Word] OR positive predictive value[Text Word] OR ppv[Text Word] OR negative predictive value[Text Word] OR npv[Text Word])).*

Search String 2: *((hiv[Text Word]) AND (self-testing[Text Word] OR self testing[Text Word] OR self-sampling[Text Word] OR self sampling[Text Word]) AND (Mhealth[Text Word] OR mobile health[Text Word] OR digital[Text Word] OR online[Text Word] OR web[Text Word])).*

Table 1: Study Characteristics of Accuracy Papers

Reference	Study Design	Country	Sample Size	Population	Digital Innovation	Intervention Description
Brady et al., 2016[1]	Cross-sectional	United Kingdom	3259	General population	Web-based (PEBLFeedback.com)	Clients bought a blood-based HIVST online and from various outlets, then were able to provide feedback on site or via an independent website (PEBLFeedback.com).
Doan et al., 2021[2]	Cross-sectional	United States	271	18–30-year-old Black and Latino MSM	Web-based	Participants ordered an oral-based OraQuick test online (recruited via ads on social media/informational sites/dating sites) conducted the self-test, then took pictures of result and uploaded to online platform where two trained researchers analyzed results.
Kwan et al., 2023[3]	Cross-sectional	China	442	18+ year old MSM	Web-based	Participants were recruited through web-based channels and could then invite their peers to participate. Implementation cascade: 1) enrolment with questionnaire completion, 2) oral-based or blood-based self-test kit request, 3) test result upload, 4) web-based training, 5) peer referral. They could also ask for real-time support, including in-person, video call, and instant messaging support, at kit request. Participants requesting real-time support received a text message through instant messaging apps to schedule a time for the self-test. A support hotline was available to all study subjects. The referees could register on the same platform and go through the same steps.
O'Byrne et al., 2022[4]	Cohort	Canada	604	General population	Web-based (GetaKit.ca)	Participants registered on GetaKit.ca and ordered a free blood-based bioLytical INSTI® HIVST to their home or designated pick-up location. Through the website, participants received a link to an online instructional video and were encouraged to report their results via the website.
Wang et al., 2020[5]	Cohort	China	279	18+ year old MSM	Multi-modal (mobile phone applications, instant messaging chat rooms, blogs, and other websites)	Participants recruited via online advertising posting in apps, instant messaging chat rooms, blogs, and other websites. Also recruited via CDC clinics or by referral of study participants. Participants used an oral-based Aware™ HIVST and self-tests were conducted on-site. At follow-up, participants were again given pre-test counselling, and could choose to perform an oral HIVST or receive a blood HIV test or both. Participants again completed a questionnaire and received post-test counselling.

Table 2: Study Characteristics of Secondary Outcome Papers

Reference	Outcome(s)	Study Design	Country	Sample Size	Population	Digital Innovation	Intervention Description
Bell et al., 2021[6]	Preference Feasibility Impact	Cross-sectional	Australia	794	18+ year old general population - focused on MSM	Web-based (HIVST online ordering webpage with links to relevant HIV-related resources and follow-up telephone interview)	A study registration page was hosted on the established QPP website, which linked to an online order system for the HIVST kit. The webpage also included links to resources relating to HIV, testing, and living positive, along with referral and support services for people newly diagnosed with HIV. Once registered, participants were offered three pre-test information options, then the oral-based OraQuick HIVST kits were sent. Two weeks after mailing HIVSTs, post-test follow-up via telephone were conducted to check if kit was received, if test was completed, whether there were issues performing/reading the self-test, result of the test, and for participant to ask any questions.
Birdthistle et al., 2022[7]	Acceptability Feasibility Impact	Cross-sectional	South Africa	3431	15–24-year-old general population	Multi-modal (MTV Shuga series on television, radio, and accompanying multimedia activities)	The participants completed an online survey, offered through Facebook, Instagram, and social media platforms of schools, universities, community groups, and clinics in Mthatha. The survey referred to their exposure to the MTV Shuga series campaign on HIV prevention including HIVST and PrEP.
Chan et al., 2021[8]	Acceptability Feasibility Impact	Cohort	China	350	18+ year old MSM	HIVST with online real-time counselling	Participants received the oral-based Aware™ HIVST kit, then made appointments through the HIVST-online administrators. Through video-chat, the administrators explained how to use the HIVST and sent them a demonstration video if needed. Pre-test counselling was provided, and participants performed the HIVST under online real-time supervision then showed the result to the administrator.
Doan et al., 2021[2]	Feasibility Impact	Cross-sectional	United States	271	18–30-year-old Black and Latino MSM	Web-based	Participants ordered an oral-based OraQuick test online (recruited via ads on social media/informational sites/dating sites) conducted the self-test, then

							took pictures of result and uploaded to online platform where two trained researchers analyzed results.
Fischer et al., 2021[9]	Acceptability Feasibility Impact	Cross-sectional	South Africa	751	18+ year old general population	Mobile app (Ithaka)	Participants received their oral-based OraQuick HIVST from an HIV South-Africa distribution and research program. Peer educators then approached participants about participating in the study - if consent was received, peer educator helped the participant log into and register for the Ithaka app on the participant's phone, where they were able to report their self-test results.
Girault et al., 2021[10]	Acceptability Preference Impact	Cross-sectional	Thailand	2504	15+ year old MSM and transgender women	Web-based	Participants were able to choose unassisted HIVST, which they performed using the oral-based OraQuick self-test. Participants were given the HIVST along with a unique identifier code used to access secure pages on the Thai-language study website with a step-by-step video on the HIVST, an online questionnaire, and a place to report results.
Johnson et al., 2022[11]	Feasibility Impact	Cohort	United States	2022	18+ year old MSM living in New York state outside of NYC	Social medias	Participants were recruited via media campaign advertisements on popular social media/networks. Those who were eligible were asked for an email address to receive a coupon that they could redeem for a an oral-based OraQuick HIVST delivered to their home for free. Follow-up online surveys took place at four to eight weeks after completion of the eligibility survey.
Kaneko et al., 2022[12]	Acceptability Impact	Cross-sectional	Japan	224	MSM	Digital vending machines	Self-administered paper-based questionnaires were completed by participants to determine the acceptability of using DVMs to distribute blood-based self-tests. Participants were divided into two groups based on whether they had ever undergone an HIV test.
Kwan et al., 2023[3]	Preference Feasibility Impact	Cross-sectional	China	442	18+ year old MSM	Web-based	Participants ordered an oral-based OraQuick test online (recruited via ads on social media/informational sites/dating sites) conducted the self-test, then took pictures of result and

							uploaded to online platform where two trained researchers analyzed results.
Li et al., 2021[13]	Impact	Cross-sectional	China	1816	16+ year old MSM	Social medias (WeChat social media platform or Blued and other social medias)	Participants paid a 7$ deposit that would be reimbursed once they uploaded their test result and followed up with post-test counselling. Blood-based HIVST were sent to participants by mail. Participants received $2 once they uploaded their test results and alters were asked to enter IPs information so those who recruited alters received an extra $3.
Marley et al., 2021[14]	Acceptability Impact	Cross-sectional	China	692	16+ year old MSM	Web-based (wjx.cn)	Participants watched a short video on a smart-phone electronic readers (SER) prototype, were given a short introductory paragraph on SERs, and were asked questions on their willingness to use the prototype for HIVST.
Mshweshwe-Pakela et al., 2022[15]	Feasibility Impact	Cross-sectional	South Africa	2267	18+ year old general population	Tablet application	Six HIVST booths were set up in two clinics (three in each) with pictorial instructions to guide the self-testing process, the oral-based OraQuick HIVST, a tablet device with the app, and headphones for participants to listen to audio content on the app. The app guided the participants HIVST process including pre-test counselling, testing with a video demonstration how to use the self-test, and post-test counselling which included next steps after a negative or positive test.
Ni et al., 2021[16]	Impact	Cross-sectional	China	1265	MSM	Web-based	Participants could order up to five HIVST (unspecified type) through the online platform. Participants (indexes) were encouraged to distribute HIVST to members (alters) within their social networks. All were given a refund once test results were uploaded.
Ntinga et al., 2022[17]	Acceptability Preference	Cross-sectional	South Africa	120	18+ year old general population residing in Vulindlela or neighbouring community	Mobile app (Nolwazi_bot isiZulu - speaking conversational agent)	Participants were left alone in the testing room and provided the oral-based BioSure HIVST kit with instructions but were asked to only use the chatbot and instructions if the chatbot said to. Individuals could choose 1/4

							personalities for their counsellor. Once prepared, the chatbot showed a video of how to use the test kit and interpret the results. Users then interpreted their result and reported it to the app.
O'Byrne et al., 2023[18]	Impact	Cross-sectional	Canada	1551	16+ years old general population-focusing on MSM and ACB	Web-based (Getakit.ca)	Participants were able to use the GetaKit website to order a free blood-based BioLytical INSTI® HIVST kit. Participants were asked to report their self-test results via the website.
O'Byrne et al., 2022[4]	Feasibility Impact	Cohort	Canada	604	General population	Web-based (GetaKit.ca)	Participants ordered an oral-based OraQuick test online (recruited via ads on social media/informational sites/dating sites) conducted the self-test, then took pictures of result and uploaded to online platform where two trained researchers analyzed results.
O'Byrne et al., 2021[19]	Feasibility Impact	Cohort	Canada	399	18+ years old general population	Web-based (Getakit.ca)	Participants registered and ordered a blood-based BioLytical INSTI® HIVST through the GetaKit website. Participants were requested to, but not required to, upload their self-test results on GetaKit.ca
Pai et al., 2021[20]	Impact	Quasi-RCT	South Africa	3095	18+ year old township populations	Mobile app (HIVSmart!)	Participants in the conventional arm were subjected to conventional HIV testing, and participants in the intervention arm conducted the oral-based OraQuick HIVST along with the support of the HIVSmart! application. Participants in the intervention arm were able to choose between a supervised or unsupervised option for self-testing. Participants were also able to upload their self-test result using the app, as well as receive linkage to care.
Phatsoane et al., 2023[21]	Acceptability Feasibility Impact	Cross-sectional	South Africa	9505	18+ year old general population	Multi-modal (mHealth system, SMS messaging)	At enrolment, participant details were entered into the mHealth system of Viamo Mobile, and participants were encouraged to conduct a short survey via recorded phone line or website to report their self-test (unspecified type) use and result. The system encouraged self-reporting through two SMS messages sent at three- and five-days post-registration. If

							not completed by day seven, an interactive voice response system called the participant to go through the survey and report their test result.
Ramos et al., 2021[22]	Acceptability	RCT	United States	322	Between 18–34-year-old sexual minority men of colour	Web-based (infographic)	Participants in the control group were given written HIVST instructions, whereas those in the intervention group were given a digital infographic pertaining to the instructions of oral-based HIVST. Participants completed the self-tests and data was collected using an online web-based survey in Qualtrics.
Rosadino et al., 2023[23]	Acceptability Feasibility Impact	Quasi-RCT	Philippines	1690	18–49-year-old MSM and transwomen residing in Metro Manila	Multi-modal (online channels of TheLoveYourself, Inc. and online messaging system)	Recruitment took place online and via online messaging systems to gather information from participants and deliver their blood-based SURE CHECK® HIVST kits. A virtual assistant system was available to participants.
Stafylis et al., 2022[24]	Feasibility Impact	Cohort	United States	254	18-30 years old MSM - Latinx or Black/African American	Multi-modal (social media, dating apps, and information search sites - leading to web-based platform for online test ordering)	Advertisements promoting free HIV self-testing were placed on social medias (Facebook, Instagram), dating apps (Grindr, Hornet), and information search sites (Google, Bing). Participants who clicked on the study advertisement and underwent eligibility criteria received a unique electronic code to order the oral-based OraQuick HIVST through Orasure.com. They were followed up 14 and 60 days after enrolment, and at follow-up, participants were asked about their HIVST use and result.
Thakker et al., 2022[25]	Feasibility Impact	Cross-sectional	India	1356	General population	Web-based (www.safezindagi.net/selftesting)	Virtual outreach workers contacted clients on dating apps and social media platforms and provided counselling. As well, directed participants to HIVST (type unspecified) via the www.safezindagi platform that allows for home delivery or pick-up at a community site. HIVST could be assisted or unassisted with pre/post-counselling from virtual workers.
Vasconcelos et al., 2022[26]	Preference Impact	Cross-sectional	Brazil	6477	18+ year old MSM	Web-based (A Hora e Agora-SP)	After participants had completed a web-based questionnaire, they were offered an oral-based

							OraQuick HIVST, free of charge. The project platform was then used to provide HIVST video instructions.
Young et al., 2022[27]	Feasibility	RCT	United States	900	18+ year old Latinx and African American MSM living in LA	Social media (peer-led online support group)	After participants had completed a web-based questionnaire, they were offered an oral-based OraQuick HIVST, free of charge. The project platform was then used to provide HIVST video instructions.
Zhou et al., 2022[28]	Feasibility Impact	RCT	China	309	18+ year old MSM	Web-based (HIVST online ordering system developed by Xutong)	An online HIVST ordering system was used, which was hosted and managed using WeChat. The study used the blood-based SD BIOLINE HIV/syphilis self-test. The control group was refunded for the HIVST, whereas the SD-M group could receive $3 per self-test, and the SD-M-PR group also could receive $3 per self-test and could refer up to 10 alters to receive a maximum of $30.

Table 3: Key Findings of Accuracy Papers

Reference	Key Findings
Brady et al., 2016[1]	**Accuracy (invalids):** Reported rate of <0.2% for invalid tests. **Accuracy (specificity)**: the rate of false positives was 3 but was expected to be 25.
Doan et al., 2021[2]	**Accuracy (agreement):** Proportion of result agreement among reviewers was 113/113 (100%, k=1.0). proportion of result agreement between reviewers and participants was 110/113 (97.3%, k=0.85 95% CI 0.67-1.0). **Accuracy (invalids):** 2/113 (1.8%) of concordant results were invalid.
Kwan et al., 2023[3]	**Accuracy (invalids):** 17/394 returned kits (4.3%) were invalid. **Accuracy (sensitivity):** Of the positive results, 2/4 were confirmed to be true positives (one was already on ART). **Accuracy (not specified):** Accuracy of the participants result interpretation was 99.1% (95%CI 97.4%-99.8%).
O'Byrne et al., 2022[4]	**Accuracy (invalids):** 81/604 participants reported 89 invalid results. 5/81 participants did not reorder a self-test. 6 participants reported 2 invalid results, resulting in 12/89 of all reported invalids (13%). Reported rate for invalid tests for all tests ORDERED was an average of 12% (0%-22%). Reported rate for invalid tests for all tests REPORTED was an average of 22% (0%-38%). Excluding the 6 participants who each reported 2 invalid tests (and 18 orders they placed), invalid tests were 9% of all ordered tests and 12% of all reported results. Invalid rate dropped after the peak in late May 2021 (when they started sending detailed instructions about completing the ST). Invalids continued to be over 10%.
Wang et al., 2020[5]	**Accuracy (all metrics):** Specificity was high, 96.8% (121/125), among MSM recruited via the internet. Sensitivity was lower, 92.9% (13/14), PPV was 76.5% (13/17), and NPV was 99.2% (121/122).

Table 4: Key Findings of Secondary Outcome Papers

Reference	Key Findings
Bell et al., 2021[6]	**Preference:** Participants reported that the reasons they chose to test for HIV via the online HIVST project were due to convenience (79%; 726), not wanting to wait for results (44%; 402), not wanting to talk about sex with anyone (33%; 298), not having time to go elsewhere for a test (29%; 268), and fear of stigma (22%; 205). Lack of local HIV testing services was reported for 7.2% (66) of orders. Of the 190 first order participants who responded to the survey question "Where would you have tested if HIVST was not available?", 21% (40) reported they would not have tested elsewhere. **Feasibility (uptake):** During the study period, 95 (14%) participants ordered two or more HIVST kits (range 2–7, median 2, interquartile range (IQR) 2–3 HIVST kits). **Feasibility (response rate):** Post-test peer worker contact with participants was achieved for 52% (485) of HIVST orders. Despite three attempts to contact participants, 48% (440) were unable to be contacted. **Impact (first-time testers):** No previous HIV test was reported by 45% (353) of first order participants. Almost one-third (31%; 123) of the men who only had sex with men reported having never tested for HIV, compared with 59% (56) of men who had sex with men and women (MSMW) (24.356, $p < 0.001$). The odds of ever having had an HIV test were decreased by 30% for MSMW (OR 0.3, 95% CI 0.2–0.5) compared to MSM. **Impact (new infections and linkage to care):** One participant reported a reactive result during the study period; with the support of the resources provided in the HIVST kit, the participant successfully self-navigated their way to confirmatory HIV testing and linkage with an HIV healthcare provider prior to the two-week follow-up call. During the follow-up telephone call, the PTF was able to link the participant with the QPP Peer Navigation Program.
Birdthistle et al., 2022[7]	**Acceptability (willingness):** Among those who had never self-tested, 83% were interested in using an HIVST, and interest in giving a ST kit to a partner was high (not specified). **Feasibility (visits to web-based provider):** Overall 43% had engaged with the campaign. **Impact (first-time testers):** Proportion of those who had used an HIVST at any point in their life (29% vs 10%; aOR=2.49 (1.95 to 3.19)) or sometime within the past year (21% vs 7%; aOR=2.61 (1.97 to 3.47)) was higher among those exposed vs those unexposed to campaign. Out of the 2694 participants who responded, 211/2094 of the unexposed and 186/645 of the exposed HAD tested for HIV using an HIV self-screening kit.
Chan et al., 2021[8]	**Acceptability (ease of use):** Out of 125 people who completed the process evaluation, 72.0%-97.6% believed that the online real-time counselling was helpful in different aspects such as understanding their current risk, testing results, concept of window period, and reducing their fear toward HIV testing and high-risk behaviours. **Feasibility (uptake):** 40.4% (92/228) of new-users and 63.1% (77/122) of ever-users received the HIVST-online during the project period. **Impact (new infections and linkage to care):** 4 HIVST-online users were screened to be HIV positive, all of who received confirmatory tested (facilitated by administrators) and were confirmed to be HIV positive. **Impact (not specified):** 16.2% of the 228 new-users of HIVST-online had NOT been tested for HIV in the past 3 years. 19.7% of ever-users of HIVST-online had NOT been tested for HIV in the past 3 years. 17.4% of all users had not tested for HIV in the past 3 years.
Doan et al., 2021[2]	**Feasibility (uptake):** 191/271 (70.5%) of participants ordered an HIVST, and 159/191 (83%) of those used it. **Impact (return rate):** 113/159 (71%) submitted readable test result images. **Impact (new infections):** 7/113 (6.2%) of concordant results were positive.
Fischer et al., 2021[9]	**Acceptability (ease of use):** Likert scores of 3.8 (SD-1.6) for "made it easy to upload results" and 4.2 (SD=0.9) for "easy to find a clinic". Reasons participants stopped using the app included used the app to completion, and unable to upload their HIVST results (2 out of 41 people said this). **Feasibility (visits to web-based provider):** 531/751 (70.7%) of participants logged on to the app. **Impact (new infections):** 14/168 (8.3%) of those who self-reported their results were HIV positive. **Impact (return rate):** 168/751 (22.4%) self-reported their results.
Girault et al., 2021[10]	**Acceptability (willingness):** 2472/2504 (98.72%) of all participants said they were interested in HIVST in the future. **Preference:** 2486/2504 (99.3%) selected HIVST vs referral to HIV testing services. **Impact (first-time testers):** 491/1422 (34.5%) of MSM and 414/1082(38.3%) of transwomen had never been tested for HIV. **Impact (new infections):** Only accounting for participants that opted for assisted or unassisted HIVST, 96/1405 (6.83%) MSM and 72/1070 (6.73%) transwomen tested positive. Among the referral group, 1/11 (9.1%) MSM and 1/7 (14.3%) of transwomen tested positive. All except one who tested positive were confirmed to be positive. **Impact (linkage to care):** Among all who needed confirmatory testing, 108/179 (60.3%) were

	referred and accessed the HIV testing services, including 5 participants who had invalid results. Of those who tested positive with confirmatory testing, 91/104 (87.5%) were linked to treatment services.
Johnson et al., 2022[11]	**Feasibility (uptake):** 922/1114 participants who redeemed the coupon and completed the follow-up survey used the HIVST kit to test themselves. **Impact (first-time testers):** 976/3197 (30.5%) of eligible participants had never been tested for HIV. **Impact (new infections and linkage to care):** 7/922 (0.8%) of those who used the HIVST for themselves tested positive, 6/7 reported they had a confirmatory test, and 5/6 self-reported they were confirmed as HIV-positive and were linked to medical care (one was waiting for the confirmatory test results at the time of the follow-up survey).
Kaneko et al., 2022[12]	**Acceptability (willingness):** Amongst MSM who had never been tested (N=37), 72.2% showed willingness to purchase tests from DVMs - even at the cost of 1000 Japanese yen. 10/37 (29.7%) knew about HIVST/postal DBS and 26 (70.3%) did not. 12 (33.3%) said they would "very much" use HIVST if it were free, 16 (44.4%) responded "pretty much", 8 (22.2%) responded "not so much", and 0 said they didn't want to. At a cost of 1000 Japanese yen, 3 (8.3%) said they would "very much" use HIVST, 19 (52.8%) responded "pretty much", 13 (36.1%) responded "not so much", and 1 (2.8%) didn't want to. Of those who had been tested before, 117/187 (63.7%) knew about HIVST and 65 (34.8%) did not. 89 (49.2%) said they would "very much" use HIVST if it were free, 51 (28.2%) responded "pretty much", 22 (12.2%) responded "not so much", and 19 (0.5%) said they didn't want to. At a cost of 1000 Japanese yen, 47 (26.1%) said they would "very much" use HIVST, 67 (37.2%) responded "pretty much", 39 (21.7%) responded "not so much", and 27 (15%) said they didn't want to. **Impact (first-time testers):** 37/224 participants had never been tested for HIV before.
Kwan et al., 2023[3]	**Preference:** At test kit request, most (338/434, 77.9%) did not opt for any support, while 18.9% (82/434), 1.8% (8/434), and 1.4% (6/434) requested instant messaging, video calls, and in-person support, respectively. Of those who accepted oral fluid tests only, they preferred getting tested for HIV in community-based organizations (OR 3.11, 95% CI 1.94-4.99, P<.001) to performing self-tests (OR 0.45, 95% CI 0.27-0.75, P=.002). The preferred modes of self-test support were instant messaging apps (77/155, 49.7%), in-person (74/155, 47.7%), and voice call (64/155, 41.3%), while video calls and chatbots were preferred by 7.7% (12/155) and 8.4% (13/155), respectively. **Feasibility (uptake):** Almost all (434/442, 98%) MSM who completed the questionnaire requested a self-test. **Feasibility (response rate):** More than half (216/354, 61%) of the eligible participants initiated the referral process by attempting the web-based training with a passing rate of 93% (200/216). Of the 200 participants who passed the web-based training, 111 (55.5%) eventually made at least one referral. **Impact (first-time testers):** 21.4% of participants had never been tested for HIV. Impact (return rate): Of those who requested a self-test, 82% (354/434) had uploaded their test results. **Impact (new infections):** Of 394 kits returned, 333 (94.1%) were negative, 4 (1.1%) were positive.
Li et al., 2021[13]	**Impact (first-time testers):** 111/394 (28.2%%) of alters and 329/1422 (23.1%) of index participants had never been tested for HIV before. **Impact (return rate):** 1816/2263 (80.25%) uploaded their HIVST result - 1422 (88.3%) index participants and 394 (21.7%) alters. **Impact (new infections):** 51/1816 (2.81%) of participants had a positive HIVST result. **Impact (linkage to care):** Of those who sought HIV care (41/51), 35/41 received an HIV-positive confirmatory result and 34/35 of them started ART.
Marley et al., 2021[14]	**Acceptability (willingness):** 493/692 (71.2%) participants were willing to use a SER, 115/692 (16.6%) were unwilling, and 84/692 (12.1%) were unsure of their willingness. 483/493 (98%) of willing participants agreed that having an SER would increase their HIVST frequency. Reasons for willingness included obtaining accurate self-test results, ease of use, and short wait time of 15-20 minutes for results. Obstacles included cost of the reader and fear of test results leaking to others. Reasons for unwillingness included never having heard of the reader, and purchase cost. Some would consider using SERs due to its ease of use and less wait time of 15-20 minutes for results. **Impact (first-time testers):** 194/692 used the HIVST for their first HIV test ever. 80/692 (11.6%) of participants had "never" tested for HIV within the past year. 156/692 (22.5%) of participants had never self-tested for HIV, and 80/692 (11.6%) had never even heard of self-testing.
Mshweshwe-Pakela et al., 2022[15]	**Feasibility (uptake):** The programme increased overall facility HIV tests by 25% (14.5% clients testing before compared to 19.9% testing during) while maintaining an HIV testing yield of 11%. **Impact (new infections):** 264/2267 (11.6%) were positive on the HIVST. 241/264 (91.3%) of those

	who tested positive received a confirmatory test and 230/241 (95.4%) were confirmed as positive. HIVST positivity yield was 12% (similar to traditional testing). The platform almost doubled the number of youths that were diagnosed with HIV (from 240 to 453). **Impact (linkage to care):** 150/230 (65%) initiated ART at the same clinic within 14 days, and 184/230 (80%) initiated ART within 9 months.
Ni et al., 2021[16]	**Impact (return rate):** 1935/1984 (97.5%) results returned, of which 648/1935 were from 625 alters.
Ntinga et al., 2022[17]	**Acceptability (ease of use):** 9/120 (7.5%) said the chatbot was easy to use. **Preference:** 95/120 (79.2%) said their HIV testing experience was much better with a chatbot than with a human counsellor, 14/120 (11.7%) said it was about the same, 7/120 (5.8%) said the experience was slightly better, and 2/120 (1.7%) felt the experience was much worse with the chatbot than that with a human counsellor. 93/120 (77.5%) said they felt as if they were talking to a real person, 15/120 (12.5%) said it did not feel as if they were chatting with a real person, and 12/120 (10%) did not respond to the question. Advantages for the chatbot included providing a safe space (no rush or judgement), offering HIV testing that is confidential, functionality, efficiency (do not have to wait at the clinic all day for results) (29/120 (24.2%) of all participants did not say any advantages when asked. Disadvantages included lack of empathy, if HIV-positive they would have the chance to hurt ("kill") themselves since they wouldn't receive the same care as a human counsellor, conversation was unidirectional, and it was easy to make a mistake (99/120 (82.5%) of all participants did not provide any disadvantages when asked. On a scale of 1-10 for preference of the chatbot, from the participants who responded (108/120), the average score was 9.32 (SD=1) ranging from 6-10.
O'Byrne et al., 2023[18]	**Impact (first-time testers):** More White (79%) than ACB participants (70%) reported prior HIV testing, whether as serology, point-of-care testing, or self-testing ($X^2 = 8.97$, $p = 0.002$). 21% of White participants, and 30% of ACB participants were first-time testers. **Impact (new infections):** There were five positive HIV self-test results reported, split evenly among ACB and White participants. **Impact (return rate):** Among the 62% (n = 962/1551) of participants who reported their HIV self-test results, more White (63%) than ACB (52%) participants reported their results ($X^2 = 12.28$, $p < 0.001$).
O'Byrne et al., 2022[4]	**Feasibility (uptake):** 604 participants ordered 701 HIVST. **Impact (first-time testers):** 25% of participants reported no previous HIV testing, and 4% were unsure if they had.
O'Byrne et al., 2021[19]	**Feasibility (uptake):** 405/600 eligible participants (67.5%) ordered an HIVST, but 6 selected "prefer not to report" so were excluded from analysis. **Impact (first-time testers):** 95/399 (23.9%) reported no primer testing and 13/499 (3.3%) were uncertain if they had ever previously been tested for HIV. **Impact (new infections):** 1/399 (0.24%) person tested positive. **Impact (return rate):** 228/399 (57.1%) of participants reported their HIVST results back through GetaKit.ca.
Pai et al., 2021[20]	**Impact (new infections):** 106/1560 (6.8%) of conventional arm and 136/1535 (8.9%) of the intervention arm (7.6% unsupervised and 10.9% supervised) tested positive for HIV. **Impact (linkage to care):** Almost all participants were linked to care (99.7% in unsupervised, 99.8% in supervised, and 98.5% conventional testing). ART for HIV-positive participants was initiated by 98.1% for intervention arm (95.7% supervised and 99.3% unsupervised) and 98.5% for conventional arm.
Phatsoane et al., 2023[21]	**Acceptability** (**ease of use**)**:** 1592/2467 (64.5%) reported the HIVST was very easy or easy to use. **Feasibility** (**response rate**)**:** In total, 2,467/9505 (26.0%) participants answered any survey question. 237 (2.5%) participants of those who had not called before day three) participants called and completed the survey after receiving the SMS reminder message on day three, and before receiving the second reminder on day five. 123 (1.3%) of those who had not called before day five called after receiving a second reminder on day five. The remaining 8,109 (85.3% of total) of participants received a phone call seven days after enrolment by the same recorded phone survey as accessed by those calling into the system. Of these, 1,777 (20.7% of those called) answered the first question of the survey. **Impact** (**new infections**)**:** Out of 314 respondents reporting an HIV positive test, 130 (41.4%) reported that this was the first positive HIVST that they had taken. **Impact (return rate):** 1,933/2467 (78.4%) of those (1933/9505, 20.3% of total) were willing to self-report their HIV status. 1,321/8109 (15.4% of those called) self-reported HIV status. **Impact** (**linkage to care**)**:** Of the 314 respondents reporting a HIV positive test, 204 (64.9%) reported that they had either linked to care or intended to link to care.

Ramos et al., 2021[22]	**Acceptability (ease of use):** 71.6% of participants agreed that the infographic was useful. 73.5% of participants agreed that the infographic was easy to use. 69.2% of participants agreed that the infographic was easy to learn. 71.6% of participants were satisfied with the infographic. Mean of "somewhat" agreeable that the infographic was useful (M=5.46, SD=1.40), easy to use (M=5.51, SD=1.23), easy to learn (M=5.41, SD 1.37) and satisfied with the infographic (M=5.34, SD=1.33).
Rosadino et al., 2023[23]	**Acceptability (willingness):** out of 4205 respondents, 4163 (99.0%) were interested in getting an HIVST. **Feasibility (uptake):** 4009/4205 (95.3%) underwent pre-qualification process, and only 2543 (60.5%) were eligible, of which only 2232 (53.1%) were unique respondents. Only 1690 participants successfully received their HIVST kit. **Impact (first-time testers):** 454/1690 (26.9%) who received the kit were first time testers. **Impact (new infections):** 93/953 participants tested positive on the HIVST (9.8%). **Impact (return rate):** 953/1690 (56.4%) reported their results. **Impact (linkage to care):** 56/93 (60.2%) were linked to further testing.
Stafylis et al., 2022[24]	**Feasibility (uptake):** 177 of the 254 participants ordered test kits during the study period. Overall, those recruited through dating apps had the highest order rate (1.24 kits/day), followed by social media platforms (0.24 kits/day) and information search platforms (0.16 kits/day). **Impact (first-time testers):** 63/254 (24.8%) participants had never tested for HIV before. **Impact (new infections):** 11 of the 131 participants (8.4%) reporting a positive HIV test result. **Impact (return rate):** 131 out of the 177 participants (74%) who used an at-home self-test kit reported a self-test result. **Impact (linkage to care):** 9/11 (82%) reported that they sought confirmatory testing and 4 of these 9 (44.4%) had started treatment for HIV. Among the 120 participants who reported a negative test result for HIV infection, 13 (11%) reported visiting a provider to discuss PrEP or reported starting PrEP.
Thakker et al., 2022[25]	**Feasibility (uptake):** 1356/2234 (61%) of registered clients ordered an HIVST. **Impact (first-time testers):** 0/43 of those who tested positive had been tested for HIV before. **Impact (new infections):** 43/1070 (4%) were HIV positive. **Impact (return rate):** 1070/1190 (90%) of those who received their kit within 3 days uploaded their results. **Impact (linkage to care):** 19/43 (44%) of those that tested positive were linked to confirmatory testing, 16/19 (84%) of who were confirmed to be positive, and 14/16 (88%) started ART.
Vasconcelos et al., 2022[26]	**Feasibility (uptake):** 1356/2234 (61%) of registered clients ordered an HIVST. **Impact (first-time testers):** 0/43 of those who tested positive had been tested for HIV before. **Impact (new infections):** 43/1070 (4%) were HIV positive. **Impact (return rate):** 1070/1190 (90%) of those who received their kit within 3 days uploaded their results. **Impact (linkage to care):** 19/43 (44%) of those that tested positive were linked to confirmatory testing, 16/19 (84%) of who were confirmed to be positive, and 14/16 (88%) started ART.
Young et al., 2022[27]	**Feasibility (uptake):** Greater proportion of those in the intervention group accepted the offer for an HIVST (29% - 130/450) compared to the control group (23% - 102/450) (OR=1.43, 95%CI, 1.04-1.95, p=0.027). **Feasibility (response rate):** 421/450 (93.4%) of the intervention group and 418/450 (92.9%) of the control group completed the follow-up survey.
Zhou et al., 2022[28]	**Feasibility (uptake):** 222 kits, 275 kits, and 337 kits were ordered from the control, SD-M, and SD-M-PR arms respectively. **Feasibility (response rate):** 96/102 (94.1%) control, 97/103 SD-M (94.2%), and 100/104 SD-M-PR (96.2%) participants did the follow-up survey. **Impact (first-time testers):** 47/309 (15%) had never tested for HIV. **Impact (new infections):** 18 people were diagnosed with HIV (15 newly diagnosed). **Impact (return rate):** 209/222 (94.1%) results returned from control group, 257/275 (93.4%) results returned from SD-M group, and 328/337 (97.3%) results returned from SD-M-PR group.

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Bridge Between Manuscripts

The previous manuscript delved into the current published works on HIVST with digital innovations, offering invaluable insights into this emerging field. Although the previous manuscript shed light on the overall benefits and impact of digital interventions in HIVST, the evidence regarding the accuracy of these interventions remains limited.

Only five papers from the last decade were identified, and among them, only one paper assessed accuracy in terms of metrics of diagnostic performance as in sensitivity, specificity, positive predictive value, and negative predictive value. Notably, the digital interventions in this study primarily focused on improving self-test uptake rather than playing a direct role in the HIVST process itself.

Keeping in mind that accuracy alone will not impact implementation of HIVST as a strategy, I also reviewed research that highlighted related aspects of implementation such as acceptability and preference, by testers, together with feasibility and impact of HIVST strategy. HIVST with digital interventions demonstrated high acceptability among individuals, characterized by a willingness to and ease of use. Encouragingly, individuals showed a promising preference for digital modes of support over non-digital methods, indicating the potential for widespread adoption of digital interventions in HIVST. The utilization of digital interventions in HIVST proved to be feasible, as evidenced by increased test uptake, improved response rates, and visits to web-based providers. Digital innovations in HIVST had a significant impact on various outcome measures, including the identification of first-time testers, detection of new HIV infections, increased self-test result return rates, and improved linkage to care.

Given these abundant findings of other outcomes, there is a pressing need for more research to evaluate the accuracy metrics of the self-testing process specifically. To address this research gap regarding the accuracy of HIVST with digital interventions, I set out to conduct a secondary data analysis of recent trial data. The primary objective was to assess the accuracy of an HIV self-test when used in combined with a digital support program, HIVSmart!, which was designed to assist individuals throughout the self-testing and linkage-to-care processes. This analysis aimed to provide evidence on HIVST accuracy with digital support, thereby highlighting the potential of digital innovations as valuable tools for increasing detection of HIV infection in communities impacted most by it.

The upcoming manuscript outlines the findings of the secondary data analysis. By evaluating test sensitivity, specificity, positive predictive value, and negative predictive value, it provides evidence supporting the improved accuracy of HIVST when digital interventions are employed. These findings hold significant implications for both individuals and healthcare providers, emphasizing the importance of digital innovations in enhancing the reliability and interpretation of test results with digital supports designed for HIVST.

Chapter III: Manuscript 2 - Exploring the Diagnostic Accuracy of HIV Self-Tests with an App-Based Readout: A Secondary Data Analysis of Trial Data

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Abstract

Background: According to the United Nations Programme on HIV/AIDS (UNAIDS), two out of every seven new human immunodeficiency (HIV) infections, globally in 2019, were among young people (aged 15 to 24 years old). HIV self-testing (HIVST) is a convenient strategy that helps increase knowledge of HIV serostatus in the young. In 2012, the Food and Drug Administration (FDA) approved the OraQuick In-Home HIV Self-Test with a reported sensitivity of 92%. Digital supports such as applications (apps) and websites, in conjunction with oral self-tests, have demonstrated a high acceptability, feasibility, and impact, yet data on accuracy with digital supports remain largely unexplored.

Methods: We performed a secondary data analysis of a quasi-randomized trial of oral-based HIVST with HIVSmart! conducted in South African township populations (2017-2019). We hypothesized that HIVSmart! guided interpretation increased test accuracy. We evaluated the diagnostic accuracy of the HIVSmart! guided interpretation of an oral self-test result against the reference standard (dual ELISA and HIV RNA), as well as compared the accuracy metrics between the supervised and unsupervised arms. Stored picture of a self-test result was uploaded by the participants via the app.

Results: Accuracy data from all 1513 HIVST participants vs. reference standard demonstrated the following:

Sensitivity = 95.52% (95% CI, 94.48%-96.56%)

Specificity = 99.93% (95% CI, 99.79%-100.06%)

Positive predictive value = 99.22% (95% CI, 98.78%-99.67%)

Negative Predictive Value = 99.57% (95% CI, 99.24%-99.90%)

No statistically significant difference of sensitivity was found between this trial data and FDA approved OraQuick sensitivity with the use of p-value comparison.

Accuracy data from 565 supervised participants vs reference standard resulted in the following:

Sensitivity: 93.65% (95% CI, 91.64-95.66)

Specificity: 100.00% (95% CI, 100.00-100.00)

Positive predictive value: 100.00% (95% CI, 100.00-100.00)

Negative predictive value: 99.21% (95% CI, 98.48-99.94)

Accuracy data from 968 unsupervised participants vs reference standard showed:

Sensitivity: 97.18% (95% CI, 96.13-98.24)

Specificity: 99.89% (95% CI, 99.67-100.10)

Positive predictive value: 98.57% (95% CI, 97.82-99.33)

Negative predictive value: 99.77% (95% CI, 99.47-100.08)

No statistically significant difference of sensitivity was found between the supervised and unsupervised arm when p-value comparison was conducted, but the incremental difference between the two groups is still worthy to note.

Conclusions: With the HIVSmart! app and OraQuick self-test, we observed an improved sensitivity of 95.5% (from 92% without an app), and specificity maintained at 99%. High positive and negative predictive values of nearly 99% demonstrate that app-based digital interpretation removed subjectivity, increased accuracy of test result interpretation, and allowed for test result recording, as well as storage of data for monitoring purposes. Findings suggest that mobile apps and readers can be useful adjuncts to improve the accuracy estimations of self-tests, obviating the need for further testing and catalyzing rapid antiretroviral therapy (ART) initiation. Although there was no statistically significant difference between the groups, the difference in

supervised vs. unsupervised arms may still support the possibility of users performing HIVST, along with digital support, better when not under the supervision of healthcare practitioners. This may be due to the stress and fear that patients experience when visiting healthcare clinics. The overall findings of this study have implications for the field of HIV and related fields exploring use of applications and readers to enhance accuracy estimations of self-testing.

3.1 Introduction

3.1.1 Background

The human immunodeficiency virus (HIV) pandemic has impacted the lives of 38.4 million individuals worldwide [1]. Despite advances in testing and diagnosis, one out of every five individuals are unaware of their positive HIV serostatus and can unknowingly transmit the virus [2]. To end the spread of HIV infection by 2030, the United Nations Programme on HIV/AIDS (UNAIDS) has set a 95-95-95 target to be reached by the year 2025 [3]. These targets state that by 2025, 95% of people living with HIV (PLWH) will know their status, 95% of those who know their status will initiate treatment, and 95% of those who initiate treatment will have suppressed viral loads [3]. HIV self-testing (HIVST) is a last mile solution to help increase the knowledge of HIV serostatus. It has been proposed as a method through which the first of the UNAIDS targets can be reached. Individuals can self-test from the comfort of their own home, thereby increasing accessibility of testing. Prior systematic reviews reported high acceptability, feasibility, and uptake of HIVST among key populations including men who have sex with men (MSM), sex workers (SW), people who inject drugs (PWID), transgender people, and people in prisons or closed settings [4, 5, 6]. A systematic review by Pant Pai and colleagues reported high acceptability and preference rates ranging from 74%-96% and 61%-91%, respectively [4]. Figueroa et al. analyzed acceptability, defined as “the willingness to take a test in the future or as an increased frequency of testing with a HIV home-test”, and reported rates above 67% [5] A meta-analysis conducted by Witzel et al. looked at the effects of HIVST compared to standard HIV testing methods for key populations [6]. In their review, they found that HIVST increased test uptake by an average of 1.45 times (RR=1.45, 95% CI 1.20-1.75) [6]. As well, HIVST

increased the mean number of HIV self-tests among MSM and transgender people by 2.56 over the follow-up period (95% CI, 1.24-3.88) [6].

Along with HIVST, digital means of intervention have also risen in popularity over the past decade. In 2023, the World Health Organization (WHO) issued a target product profile for readers of rapid diagnostic tests, in which they define "a dedicated hardware instrument or an app that operates on a general-purpose mobile device such as a tablet or phone", which may be used in screening and diagnostics to support proper test performance [1]. A systematic review conducted by McGuire et al. analyzed the acceptability of digital self-testing methods worldwide [7]. Social media and mobile application (app)-based HIVST methods were found to have an average acceptability rate of approximately 91%, ranging from 87% to 95%, supporting the popularity of digital HIVST methods [7].

In 2013, an application called HIVSmart! was developed by Dr. Pant Pai and her team. This digital method is integrated into the HIV self-testing process and guides patients through their HIVST experience. The application also connects patients to continued care, including counselling resources and confirmation of test results.

There is a paucity of research regarding whether the accuracy of HIVST can be optimized by digital supports or solutions. In the post-COVID era, the price of these self-tests is on a decline, and the use of digital applications and platforms is on the rise, which shows promise for increasing digital HIVST. Accuracy is estimated using standard metrics of sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV). In 2012, the OraQuick In-Home HIV Test was approved by the Food and Drug Administration (FDA) on the company's report of an average sensitivity rate of 91.7% and a specificity rate of 99.9% [8]. Thereafter, studies reported accuracies ranging from 87.5%-99.5% sensitivity and 98%-100%

specificity for the OraQuick self-test compared to reference standard [9, 10, 11]. These high sensitivity and specificity rates are promising evidence of the reliability of the OraQuick self-test. Despite this, performance of self-tests integrated with digital solutions and the consequent impact on test accuracy has not yet been investigated.

Currently, about 20% of all PLWH reside in South Africa, where 7.5 million people are HIV-positive [12]. In 2023, HIVST kits have become easily accessible in South Africa [13]. Due to the popularity of these self-tests, the effect of digital innovations, such as HIVSmart!, that work with self-tests to enhance their conduct, counselling, and linkage to care have also risen in popularity.

The original trial from which this data was collected was conducted in South Africa between 2017 and 2019 [14]. Within the context of this trial, we were motivated to examine how the use of the HIVSmart! application improved the accuracy of HIV self-tests and to what extent. With a greater use of readers and digital applications being recommended by the regulatory bodies for point-of-care tests, it is important to ascertain the degree of incremental difference they make to eliminate the subjectivity experienced by users during self-test interpretation. The results of this study serve to impact policy and future research for digital self-testing integrated solutions. HIVSmart! is a prime example of an innovative tool that can be used to improve HIVST readout by users, which is why such solutions should be considered to aid in achieving the UNAIDS 95-95-95 targets by 2025.

3.1.2 Study Objective and Hypothesis

The objective of this study was to evaluate the diagnostic accuracy of HIVSmart! for oral self-test result interpretation against the reference standard of two blood-based rapid tests and a

lab-based HIV RNA test. We also analyzed the difference in accuracy readouts between the supervised and unsupervised arms of those who self-tested.

We hypothesized that the self-testing method along with HIVSmart! that guides participants through the process of self-testing, result interpretation, together with counselling, will result in an increase in accuracy, including sensitivity, specificity, PPV, and NPV, compared to the use of self-tests without digital aids, measured by the self-test accuracy metrics currently indicated by the FDA [8]. As well, we predict that those in the supervised arm will receive higher accuracy metrics, considering they are supported by healthcare professionals and the HIVSmart! app. Alternatively, we hypothesized that the unsupervised self-testing strategy will be better support with the app, whereas the supervised will be supports more so by the healthcare workers.

The primary outcome of this analysis was to explore the performance ability of the HIVSmart! guided self-testing process, which includes a stored picture of a self-test result by the participant, versus the reference standard test result, and to measure the difference between the supervised and unsupervised arms.

3.2 Methods

3.2.1 Study Design

We conducted a secondary data analysis of 1535 participants who were enrolled in the intervention arm of the quasi-randomized controlled trial conducted between 2017 to 2019 [14]. 1513 participants were included in the final analysis, considering those with missing self-test or confirmatory testing results were excluded. As well, those who did not wish to use the HIVSmart! app through the self-testing process were excluded from the final analysis.

The original trial successfully evaluated the clinical and public health impact and effectiveness of the HIVSmart! self-testing strategy on new infection detection and linkage to care in township populations in South Africa. Details of the original trial can be found here in the PLOS publication [14].

3.2.2. Participants and Setting

Eligibility criteria of participants included being 18+ years of age, having an unknown HIV status at baseline, and having access to an Android/iPhone smartphone or the ability to use a tablet/smartphone for self-testing via HIVSmart!. Participants were recruited to participate in the study if they had presented for HIV testing at community outreach clinics in Cape Town, South Africa and had met the eligibility criteria.

Clinic staff also recruited participants during routine and drop-in visits. Recruited participants were then encouraged to refer their partners, friends, and family; individuals who were referred were able to participate in the study if they fit the eligibility criteria. As well, community outreach was accomplished by healthcare workers, word of mouth, handouts/flyers, demonstration videos in the clinics, a Facebook page, and radio/television announcements. Potential participants were excluded from the study if they were on ART, had a confirmed HIV diagnosis, or had a serious medical condition that required hospitalization.

All districts in Western Cape Town were geomapped and a random number sequence was generated in STATA V.12. Within each of the three geographic sampling frames, two geographically separated clinics were then randomly sampled for a total of six clinics' participation. Participants were offered the choice of performing the self-test supervised at the clinic, or unsupervised at the clinic or a location of their choosing.

3.2.3 Test Methods

After providing informed consent, the participants could choose to undergo the supervised or unsupervised self-testing strategy. In both strategies, the participants first received a brief introduction to the app-facilitated self-testing process, and then they conducted the self-test in the clinic (supervised testing) or other spaces (unsupervised testing – including office, home, mall, or kiosk). Before the participant left the clinic, reference standard tests were performed. These consisted of two rapid finger-prick blood tests, followed by an HIV RNA laboratory test.

Pre-test counselling was offered through the HIVSmart! app and participants performed the OraQuick rapid HIV-1/2 self-test (OraSure Technologies Inc, USA) usually within the same day as reference tests. If the participant chose the unsupervised option and took the test home, they were instructed to complete the test and provide results within 24 to 48 hours, which each participant successfully executed. All self-tests were completed with the assistance of HIVSmart!. The self-test interpretation was also performed with the help of HIVSmart! and recorded on the app.

To conduct the self-test, the participant collected oral fluid samples by pressing the flat pad of the test kit into their mouth and swabbing around the upper and lower gums, then placing the flat pad into the tube of buffer liquid and letting it sit for 20 minutes before reading the result.

A positive result would show two lines on the test device (one control line and one test line), possibly including a faint test line, whereas a negative result would appear as one control line. Invalid results were defined as the appearance of a faint test line only, or no lines, and were obtained by few participants, but were not included in the final analysis. If any indeterminant results were found from one of the two rapid tests, a third rapid test was performed before the lab

confirmatory test. As well, indeterminate reference standard tests were handled by the phlebotomist and were then repeated.

The HIVSmart! app supported participants through their testing process. Participants were first introduced to the "virtual clinical assistant" who walked them through preliminary information, the HIVST steps, and post-testing support. Before testing, participants were asked to answer a few questions about their sociodemographic characteristics. Once completed, the app provided evidence-based information on what HIV and acquired immunodeficiency syndrome (AIDS) are, how it could be contracted, who may become infected, testing options, why to get tested, what a self-test is, and what to do once your self-test result is received. After this informative pre-test counselling section, the virtual assistant completed a risk assessment evaluation through a small set of questions and provided a result at the end to let the participant know their risk score. Details regarding the risk scores captured during this study are available in recent publications [15, 16]. After the risk score assessment, the test procedure was explained by the app-based assistant, and an instructional video of 20 minutes was then provided for the participant to conduct the self-test, during which the participants were presented with questions to keep them engaged. These questions were referring to their self-testing experience and preferred method of linkage to care and follow-up care.

When the 20 minutes of testing had passed, the app displayed images of the self-test results and asked the participants to choose which most resembled their test result, which mitigated the uncertainty of test interpretation. The user also had the option of scanning the test with the device's camera and uploading a picture of their self-test result. Either or both options were used for interpreting their result. Self-test results were then compared to the reference tests and HIV status was confirmed for the participant by the counsellor, immediately followed by

linkage to post-test counselling options. These included a direct app-built phone line to a counsellor nearby, linked to the University of Cape Town, and options for participant preferred clinics providing care in their region.

The readers of the reference standard test, such as healthcare staff and researchers, were not blinded to the results of the index test with the app. As well, clinical information was available to the assessors of the reference standard test only for participants in the supervised group, but not within the unsupervised group. All collected personal data was deidentified and encrypted to conserve the anonymity of participants' identities throughout the statistical analysis.

3.2.4 Statistical Analysis

Given that self-test accuracy was aimed to be 92% sensitivity and 99% specificity, as following the FDA metrics, a sample size of 1250 was deemed sufficient for the self-test with HIVSmart! estimations.

The secondary data analysis was conducted using STATA V.17 to determine the Sn, Sp, PPV, and NPV of the digital HIVST result versus the HIV confirmed status (two rapid tests and the lab test). As well, the separate accuracy metrics between the supervised and unsupervised arms were calculated to analyze the impact of supervision on the participant's test accuracy. These values were then compared to confirm the relationship between self-tests and the reference standard. A T-Test of proportions was conducted using Microsoft Excel to evaluate the difference in proportions of positives between two samples and p-values were reported.

3.2.5 Ethics Approval

The original study by Pant Pai and colleagues was approved by the Institutional Review Board of the Research Institute of McGill University Health Centre and the University of Cape Town. All participants of the trial gave written informed consent to participant in the study.

Ethics approval for this secondary data analysis was obtained as part of an extension to the primary study.

3.3 Results

3.3.1 Participant Demographics

Of 1535 consenting participants that had reference test samples collected on the same day as their recruitment, a vast majority (n=962) chose the unsupervised option for self-testing (Figure 1). However, eight participants in the supervised arm and 14 participants in the unsupervised arm were excluded from the analysis since they did not have either a self-test or lab confirmatory result available. The mean age of the participants was 28 years old (range: 19-37), a majority of which were female (64.76%). Participants in the supervised arm conducted the self-test before the reference standard sample was collected at the clinic, and those in the unsupervised arm reported their self-test results within 24 to 48 hours of reference testing. Other demographic and baseline characteristics are presented in the published article of the initial trial data [14].

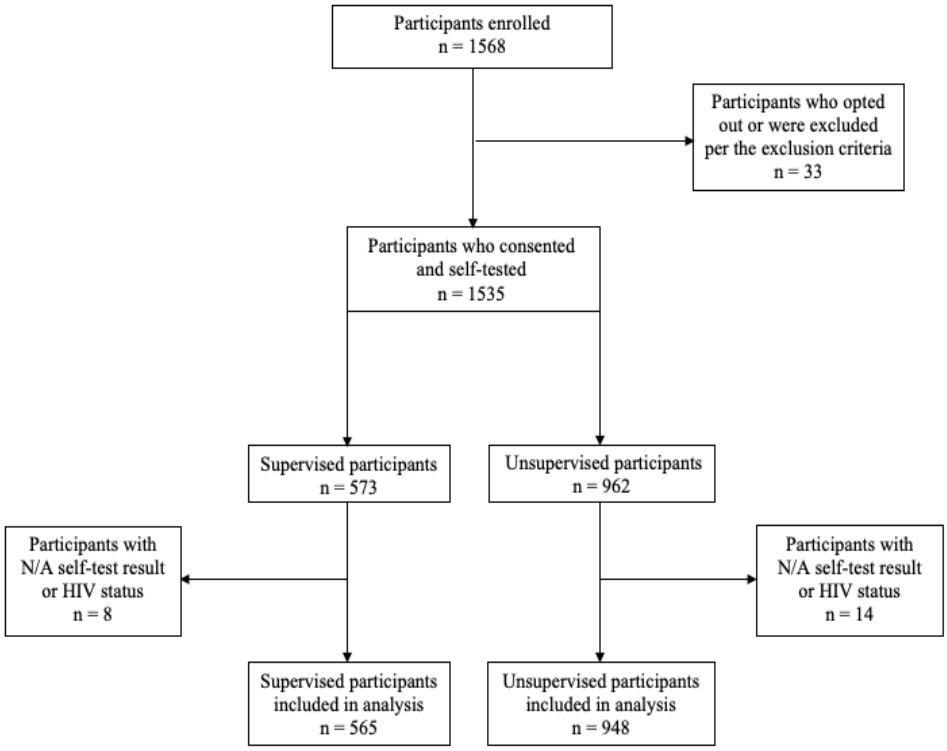

Figure 1: Flow diagram of participants

3.3.2 Test Results

The analysis we conducted was to test the accuracy of the self-test result obtained when performed along with HIVSmart!. Considering both rapid and lab tests were performed, both were used as the HIV confirmed status and analyzed for sensitivity, specificity, PPV, and NPV in reference to the HIVST result. Adverse effects from the self-test, rapid tests, or laboratory sample were not reported by any participants.

Comparing the self-test result, performed with the HIVSmart! app, the Sn was 95.52% (95% CI, 94.48-96.56), Sp was 99.93% (95% CI, 99.79-100.06), PPV was 99.22% (95% CI, 98.78-99.67) and NPV was 99.57% (95% CI, 99.24-99.90) (Tables 1 and 2).

Comparing the calculated sensitivity value with the FDA approved sensitivity value, there was no statistically significant difference between the two (p-value = 0.72).

For participants in the supervised strategy, the estimations were Sn: 93.65% (95% CI, 91.64-95.66), Sp: 100.00% (95% CI, 100.00-100.00), PPV: 100.00% (95% CI, 100.00-100.00), and NPV: 99.21% (95% CI, 98.48-99.94) (Tables 3 and 4).

For participants in the unsupervised strategy, the estimations were Sn: 97.18% (95% CI, 96.13-98.24), Sp: 99.89% (95% CI, 99.67-100.10), PPV: 98.57% (95% CI, 97.82-99.33), and NPV: 99.77% (95% CI, 99.47-100.08) (Tables 5 and 6).

The T-Test used to compare the sensitivity values between the supervised and unsupervised groups found there to be no statistically significant difference between them (p-value = 0.66); however, an incremental difference of 3.53% in sensitivity was noted.

Table 1: ST+HIVSmart! versus lab-confirmed HIV for participants

		Lab-Confirmed HIV		
		+	-	Total
ST+HIVSmart! Result	+	128	1	129
	-	6	1378	1384
Total		134	1379	1513

Table 2: Overall diagnostic performance of HIVST in participants

	Value (%)	**95% Confidence Interval (%)**
Sn	95.52	94.48-96.56
Sp	99.93	99.79-100.06
PPV	99.22	98.78-99.67
NPV	99.57	99.24-99.90

Table 3: Supervised arm performance: ST+HIVSmart! vs. lab-confirmed HIV status

		Lab-Confirmed HIV		
		+	-	Total
ST+HIVSmart! Result	+	59	0	59
	-	4	502	506
Total		63	502	565

Table 4: Diagnostic performance for supervised arm

	Value (%)	95% Confidence Interval (%)
Sn	93.65	91.64-95.66
Sp	100.00	100.00-100.00
PPV	100.00	100.00-100.00
NPV	99.21	98.48-99.94

Table 5: Unsupervised arm performance: ST+HIVSmart! vs. lab-confirmed HIV status

		Lab-Confirmed HIV		
		+	-	Total
ST+HIVSmart! Result	+	69	1	70
	-	2	876	878
Total		71	877	948

Table 6: Diagnostic Performance for unsupervised arm

	Value (%)	95% Confidence Interval (%)
Sn	97.18	96.13-98.24
Sp	99.89	99.67-100.10
PPV	98.57	97.82-99.33
NPV	99.77	99.47-100.08

3.4 Discussion

3.4.1 Key Findings

Accuracy of self-tests is captured by sensitivity and specificity. Sensitivity of the oral-based OraQuick self-test along with HIVSmart! was 95.52% for all participants. However, unsupervised strategy reported a higher sensitivity of 97.18% versus supervised at 93.65%. Specificity of the combination was stable (overall 99.93%; supervised 100%, unsupervised 99.89%).

In 2012, when the FDA approved OraQuick, the package insert with the self-test alone reported sensitivity as 91.7% and specificity as 99.9% [8]. In our study, we found an increment in both: sensitivity of 95.5% and specificity of 99.9%. The difference was not found to be significantly different, however it is still important to consider when looking at the population level since this can translate to many more false positives being accurately interpreted as true positives using digital supports compared to without.

Together with the app, both positive and negative predictive values were found to be at least 98.5%. Increased PPV and NPV are further comfort to patients that the result they receive is an accurate representation of their HIV serostatus. This means that the use of the HIVSmart! app together with the self-test improves the reliability of self-testing.

Dividing the results to analyze the supervised and unsupervised arms individually yielded very fascinating results. The specificity, PPV, and NPV were all moderately similar, but the sensitivity rate was 93.65% for the supervised participants, compared to 97.18% for unsupervised participants. Although this difference was found to be statistically insignificant, it is still important to consider, given that at the population level, this statistic equates to an increased number of HIV-positive individuals knowing their true status when using HIVSmart! to conduct HIVST in complete privacy. This is an extremely interesting result, with the unsupervised arm having a 3.53% sensitivity increase, considering it is likely to be assumed that one would conduct a self-test more precisely with the supervision of a healthcare professional. A possible explanation for this outcome is that the participants who chose the unsupervised option were more comfortable in their ability to conduct the self-test alone. As supported in past research, participants in healthcare research can dislike practitioners, especially in the case of HIV due to stigma and judgement [17]. These results mean it is possible to infer that the use of

HIVSmart! on its own, without any practitioner support, is sufficient in supporting patients through the self-testing process and negates any anxiety some may feel with healthcare workers.

3.4.2 Other Research

Given the novelty of self-testing digital innovations, it is not surprising that previous studies have shown intriguing results regarding HIVST accuracy, but not analyzed the impact that digital supports have on test accuracy.

A cross-sectional study conducted by Martinez Pérez and colleagues investigated how accurate the OraQuick In-Home HIVST was among rural populations in South Africa [18]. This study did not include a digital support. Participants were asked to complete the oral self-test under the supervision of a counsellor, followed by blood based rapid tests (Determine™ and Unigold™) as the reference standard. The sensitivity was reported as 98.7% (95% CI 96.8-99.6) and the specificity was calculated to be 100% (95% CI 99.8-100). PPV and NPV were determined to be 100.0% (95% CI 98.2-99.9) and 99.7% (95% CI 99.4-99.9) respectively [18]. These high values are supportive evidence of the OraQuick test's accuracy; however, these tests were conducted under the supervision of a counsellor and were compared to rapid blood-based tests instead of a laboratory-based result. It can be assumed that the accuracy metrics would decrease if the self-tests were conducted alone, but with the support of digital interventions, these metrics can be maintained or even increased. In real-life settings, self-tests tend to be done in private and especially when it comes to the stigma of HIV, the autonomy of conducting a self-test in one's preferred privacy setting is an important aspect. To protect this sense of autonomy and the high self-test accuracy in professional settings, digital innovations such as HIVSmart! should be used.

A paper by Stevens and colleagues reviewed global studies conducted before November 2015 that evaluated the sensitivity and specificity of the OraQuick Rapid HIV-1/2 oral test and other HIV self-tests [19]. These studies found an overall median sensitivity and specificity of 93.6% and 99.9% respectively [19]. However, it is notable that one of the studies from this review did not include faint or weak positive lines as positive test results. Based on these findings, it appears the specificity of these tests has remained stable over time, but the sensitivity is improved with HIVSmart!. Sensitivity is a key parameter for it allows us to be safe in knowing that the positive test results are indeed positive; therefore, with HIVSmart!, less than 5% of self-test results are misclassified as false negatives.

This review also mentions the ability for participants to perform oral- and blood-based self-tests [19]. A study by Peck et al. found that less than 25% of participants were able to conduct the self-test correctly and 47.3% of all participants made multiple errors, when unsupervised [20]. These were also performed without digital supports like mobile apps or websites. In terms of self-test result interpretation, only 79.7% of negative results and 78.7% of strong positive results were correctly interpreted [20]. Unfortunately, only 26.7% of the faint positive results were correctly interpreted by the participants who received this result [20]. Conducting the test and interpreting the results are aspects of self-testing that can be improved with HIVSmart! and other digital health technologies.

A third study by Ng et al. analyzed the accuracy in the OraQuick self-tests performed by untrained individuals alone compared to with trained healthcare workers [21]. The untrained individuals performed the test with an 11-step package that was designed by the study team and replaced the OraQuick test insert. The package included instructions on kit preparation, collection of oral fluids, specimen insert into the buffer fluid, and result interpretation. As well, a

sheet with seven images of the possible ranging results were provided to participants, likely increasing result interpretation. This study found the self-test sensitivity and specificity to be 97.4% and 99.9% respectively [21]. Importantly, the k-value for inter-rater agreement between the self-test and test with healthcare worker was found to be 0.97, meaning there was very similar results concluded by the participants conducting the self-test alone and then with the healthcare worker. These results are very similar to what we obtained with HIVSmart! as compared to the reference standard, implying that the pictorial interpretation allows for improvement in accuracy readout compared to unsupported interpretation. With the use of readers recommended by the WHO/Foundation for Innovative New Diagnostics (FIND), we will improve the estimations of accuracy with mobile applications in the near future [22].

3.4.3 Limitations

Although the findings of this study are promising, there are a few limitations that may have impacted the determined results.

An example of this is that the participants only conducted the self-test once, which may hinder the reliability of the test results. If the self-tests were repeated, there is a possibility that the same status would not be obtained a second time. On the other hand, repeating the self-tests could have improved users' testing method and using only the second-test results could have produced a lower number of indeterminate tests, which would increase the accuracy metrics. It is difficult to say what would happen if the self-tests had been repeated, but for test-retest reliability, this should have been considered if viable. This study was part of a trial, so it was unfortunately not possible to repeat self-tests given that it would inflate the cost of testing.

As well, participants were offered a choice to conduct the self-test alone or with supervision, therefore randomization was not possible and selection bias may have played a role

in the results. One would believe that confounding could have played a role in demographics and choice, although statistically significant differences between the two groups was not found [14]. However, an unexplored factor here is the confounding effect of culture and religion. Considering the stigma around HIV and homosexuality, those with a religious background may have been more likely to choose the supervised option and been able to conduct the test in the safe environment of the clinic, instead of at their homes. This may be reflected by the fact that those who chose the supervised option were older and had more co-morbidities [14].

Finally, another possible limitation is related to the generalizability of these results. The study population consisted of township populations, who were particularly at risk of contracting HIV. Although we could generalize it to township populations with similar demographics across Southern African region, these findings may not be applicable to the general population of South Africa.

3.4.5 Implications for Practice

The use of digital innovations with self-tests increases the accuracy of the test result, and the predictive value of the test result. This helps improve confidence in the self-test results and that improves the value proposition of the solution.

Despite the study limitations, a major benefit of the study was that the flexibility and choice of venue maintained high participant engagement and resulting in a retention rate of 97.9%, which is the highest to date reported with an app-based solution. The high retention rate, along with great accessibility and flexibility, and high accuracy increase the likelihood of acceptance of this solution.

Relative to current clinical processes, HIVST and the HIVSmart! app should be viewed as complementary means to current practices. Once a self-test result is obtained, the patient may

choose to seek confirmatory tests, through the app, if they desire. Considering the high specificity rate of this test with the application, those with negative results will likely not require a confirmatory result, therefore saving laboratory testing supplies for those who are suspected to be HIV-positive. As well, the accessibility and sense of autonomy that are associated with self-testing and HIVSmart! will likely encourage patients to recommend this testing option to others in their social circles, hopefully increasing the uptake of HIVST and in turn, increase serostatus awareness. With user consent, the use of HIVSmart! can allow self-test results to be safely recorded for data collection, which may benefit future educative applications to further increase the accuracy of self-test interpretation by patients.

The originality of this work will pave the way for upcoming research in accuracy with the support of digital innovations.

3.5 Conclusion

HIVSmart! is a promising digital innovation that allows patients to choose preferred language options, watch simple videos for testing directions, and access continuative care directly through the application as soon as their final test results are relayed. In addition, data collection via HIVSmart! is beneficial for further studies to guide in improving self-tests and interpretation by patients. In the future, we may be able to expand on this concept to use molecular tests and readers that would remove the subjectivity experience in interpretation entirely.

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Chapter IV: Discussion

4.1 Key Findings

The findings of the first manuscript provide evidence of the several measurable benefits of HIVST with digital supports. Digital innovations have demonstrated positive influence on various aspects of HIVST including accessibility, preference, feasibility, and impact. Digital means of support in the HIVST process led to high acceptability presented as willingness and ease of use percentages. The study by Girault et al. demonstrated a high willingness to use HIVST, with a percentage as high as 98.72% [21]. As well, the paper by Chan et al. highlighted that 97.6% of participants found digital means of support improved their understanding of their test results, which is crucial for effective self-testing [10]. When compared to traditional reference standards of testing, digital innovations in HIVST showed promise in terms of the general population's fondness for this form of support.

Various indicators of feasibility were positively evidenced as well. For example, the paper by Young et al. (2022) showed that online support increased test uptake by 6% compared to when it was not provided [22]. The same study also found a higher response rate among the intervention group compared to the control group. Additionally, the study by Fischer et al. (2021) demonstrated satisfactory interaction with web-based providers, reaching a percentage of 70.7% [13].

The significant impact that digital methods of intervention play on the HIVST process were made evident in terms of new HIV infections, first-time testers, self-test return rates, linkage to confirmatory testing, and linkage to treatment. HIV infections were analyzed by majority of the papers included in the analysis and prove that HIV self-testing methods do support the findings of new HIV infections which will contribute to the increase in serostatus awareness [21, 22, 24,

25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38]. First-time testers were also reported by many papers and found HIVST to be a viable means of reaching those who have not previously tested for HIV [21, 25, 26, 29, 31, 32, 36, 39, 40, 41, 42]. Self-test return rates were made more accessible by digital means [24, 25, 27, 29, 31, 32, 33, 35, 34, 37, 38, 43]. Considering patients can simply upload their test-result through digital innovations, such as apps or websites, which improves convenience for the users.

Linkage to care is also significantly improved with digital innovations, notably found in the papers by Pai et al. and Li et al. due to the increased convenience of healthcare accessibility via web-based and app-based support [29, 34] Finally, and most importantly, accuracy was reported by a few studies but there is a need for more evidence in this field. Promisingly, the study by Wang et al. reported high sensitivity, specificity, positive predictive value, and negative predictive value for HIVST, demonstrating its improvement in accuracy of the combined testing method [44].

The second manuscript of the secondary data analysis that was conducted provides evidence that digital innovations can increase accuracy metrics in HIVST. In particular, the use of HIVSmart! support demonstrated increases sensitivity and comparable specificity compared to the FDA-reported metrics of the OraQuick self-test when used alone. By leveraging digital innovations like HIVSmart!, individuals undergoing HIVST can be reassured of an accurate test result with 100% PPV and NPV of 100%. These results are powerful by implying that a positive self-test is likely to be positive if additionally read by an app, and a negative self-test is likely to be negative, almost reducing the need for additional confirmation with rapid tests. Therefore, the tester can safely be recommended to start therapy if they test positive, and prescribed PrEP, or other preventative measures, if they test negative.

With a digital program, the tester can benefit from additional support, guidance, and educational resources that enhance the accuracy of their test results. These digital interventions have the potential to improve overall testing outcomes and contribute to effective HIV serostatus awareness.

The overall findings of this thesis regarding digital innovations in HIVST provide evidence of the improvement they can bring to the self-testing process. The key focus of this thesis was the significant enhancement of accuracy in self-test results, which can provide reassurance to users regarding the reliability of their HIV serostatus. The incorporation of digital innovations in HIVST has shown to improve the overall testing process. These innovations offer additional support, guidance, and resources to users, resulting in various benefits. The increased accuracy provided by digital innovations can offer users greater confidence in the results of their self-tests. Knowing that their test results are more likely to be an accurate representation of their HIV serostatus can help alleviate concerns and uncertainties. By leveraging digital tools and interventions, individuals engaging in HIVST can have a more reliable and accurate testing experience. This improvement in accuracy contributes to the overall effectiveness of HIVST programs and promotes a better understanding of one's HIV serostatus, which is vital for individual health and the prevention of HIV virus transmission.

4.2 Future Directions

While various aspects of digital HIVST have been researched, the emphasis should now shift towards evaluating the impact of digital innovations on accuracy; this will help establish the role of digital interventions in improving the reliability of HIVST. The provided research paves the way for future studies to examine the accuracy of HIVST with digital innovations in terms of

diagnostic performance parameters such as sensitivity, specificity, positive predictive value, and negative predictive value.

Ideal study designs for future research would involve randomized control trials (RCTs) that compare the effect of digital innovations in HIVST to no digital support on all outcomes including accuracy. These trials would have a control arm where HIVST is conducted without digital intervention, and an intervention arm where self-testing is conducted with digital support. Analyzing the odds ratio between the two groups would quantify the difference in accuracy performance attributable to digital innovations. Comparing accuracy metrics between the two groups (with vs. without digital) will allow us to find the incremental difference in diagnostic performance. In a high prevalence setting, this will translate to fewer false negatives, therefore improving sensitivity. This evaluation will also increase confidence in digital methods and that will translate to more individuals using these methods.

Image analyses is an upcoming field in machine learning, and our findings inform the development of tools in this area for future iterations of self-tests and for self-test in related fields such as Hepatitis C virus, Syphilis, COVID-19, and others.

If we could pool data from all the applications around the world that have used one brand of oral self-tests or another brand of blood-based self-tests, we can explore variability in accuracy between populations a bit more. This exploration will entail applying deep learning to better predict a positive result and a faint positive result that precipitates confusion in the minds of self-testers. These developments are germane to informing the future of digital diagnostics.

Once many RCTs have been conducted worldwide, conducting individual patient data meta-analyses and systematic reviews to summarize the findings would be highly valuable. These

analyses would provide a comprehensive overview of the impact of digital innovations on HIVST accuracy across multiple studies. Such insights can influence policy-making decisions and guide healthcare systems in implementing effective strategies not just for HIVST, but also for related co-infections. By conducting rigorous RCTs and synthesizing the findings through meta-analyses and systematic reviews, the scientific community can gain a deeper understanding of the benefits and impact of digital innovations in HIVST accuracy. This knowledge will be crucial for informing policies and improving healthcare practices. Additionally, this knowledge will also help maximize the potential of digital interventions in promoting HIV serostatus awareness and prevention of HIV transmission in communities deeply impacted by the pandemic.

4.3 Conclusion

In conclusion, digital innovations not only play a significant role in improving the acceptability and preference of HIV self-testing compared to lab-based reference standard tests, but also increase feasibility and lead to a stronger impact on important outcomes of HIV testing. My analysis shows that it helps improve accuracy measurements, thereby improving their diagnostic performance, that will comfort users in knowing their self-test result is accurately reflective of their HIV serostatus.

With the drastic evolutionary steps being made in the technological world, such as artificial intelligence, it only makes sense for such methods of healthcare to follow suit in the near future.

Digital tools that are nearly 100% accurate are not only promising for the field of HIV diagnostics, but for all forms of self-testing. If digital innovations become a normalized aspect in

self-testing, the world of screening and diagnostics will be irreversibly transformed for the greater good of affected populations worldwide.

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