The Economic Impact of Case Finding for Infectious Disease in a Global Health Context

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Abstract

Despite advances in recent years, human immunodeficiency virus (HIV) and tuberculosis (TB) are major contributors to global morbidity and mortality. Progress in mitigating the spread and impact of both infectious diseases is being made in many settings, but there is an ongoing gap in hard- to-reach and marginalized populations. Early diagnosis and treatment of infectious diseases is a core component of global efforts to mitigate infectious disease burden. The cost effectiveness of enhanced screening throughsystematic screening and self-testing (ST) is imperative prior to scaling up these programs given the reality of finite resources within any health care setting.

We have undertaken a systematic review to summarize the current economic literature around systematic screening for active TB and ST for HIV. The inputs from the HIVST systematic review were used to create a combined decision tree and Markov model to evaluate the cost utility of HIVST along with digital and community-based programs to support downstream linkage to care.

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Introduction

Despite advances in recent years, infectious diseases are a major contributor of morbidity and mortality globally[1]. Progress in mitigating the spread and impact of infectious disease is being made in many settings, but there is an ongoing gap in hard to reach and marginalized populations[2-4].

Based on the most recent Global Burden of Disease data from 2017, both human immunodeficiency virus (HIV) and tuberculosis (TB) are among the top ten global causes of mortality[1]. UNAIDS reported in 2020 that approximately 37.7 million people globally are living with HIV, with 1.5 million new infections[5, 6]. The World Health Organization (WHO) reported that in 2019 there were 1.4 million TB-related deathsand 10 million new infections[7].

HIV and TB have treatment options; HIV is treated by antiretroviral therapy and TB is treated with an oral antibiotic regimen. For people living with HIV (PLHIV) treatment decreases viral load and progression to acquired immunodeficiency syndrome (AIDS), which is associated with opportunistic secondary infections and death[8]. For the majority of individuals affected with TB, treatment is curative,while untreated active TB is associated with a 20-30% risk of death[9]. Early and effective treatment of HIV and TB has the potential to prevent further infectious transmission throughout the community.

Leading institutions of global health have set ambitious targets such as the UNAIDS 95/95/95 goal[10] for HIV and the WHO ENDTB strategy[11] that have emphasized early diagnosis and treatment as a key component of targeting the spread of infectious disease. For both HIV and TB, there are strong socioeconomic factors that influence the risk of infection, diagnosis and treatment. HIV is a blood borne infection and can be spread through the exchange of bodily fluids with an infected individual. This may occur through shared needle use, blood product

contamination, breastfeeding, maternal-fetal transmissionand sexual intercourse[12]. High risk groups for HIV infection include individuals requiring frequent blood transfusions, sex workers, men who have sex with men (MSM) and intravenous drug users (IVDU)[13].

Tuberculosis is contracted through airborne transmission. Risk factors to contract TB include crowded housing, immunosuppression and proximity to another individual with TB[14-16]. Both TB and HIV show variation in their geographic distribution with certain regions having higher endemic rates than others. For HIV and TB, high-risk subpopulations may experience significant barriers to accessing health care. Previous literature has suggested that discrimination, mental health comorbidities, financial means and physical distance are all important factors that can impact access to conventional health care[17-19]. Traditionally, diagnosis of infectious diseases has been facility based and required an individual to self-present to a health care facility for diagnosis and treatment. This represents passive case finding (PCF), which is the standard of care for infectious disease diagnosis. The key principle of systematic screening is that individuals are screened before self-presenting to the health care system with symptoms of active disease. Systematic screening, when paired with early treatment initiation, has the potential to decrease asymptomatic infections and spread throughout a community[20]. Self-testing has been studied in avariety of different infectious diseases and means that the individual can conduct an initial screening test prior to confirmatory diagnostic testing. This can be done in a variety of different ways including urine, sputum and blood-based testing methods. Self-testing can occur in a variety of settings including within a clinic, community organization or at home[21]. Self-testing provides a method of promoted local, community-focused testing which might provide a means to improve accessibility of screening to high- risk populations.

Previous literature has established that both systematic screening and self-testing are effective in a varietyof settings and have the potential to improve screening uptake[22-33]. Given the reality of

finite resources within any health care setting, it is imperative to ensure that interventions are also cost effective to maximize overall population health.

To better understand the economic landscape and potential impact and cost-effectiveness of systematic screening in TB and self-testing approaches for HIV we undertook several discrete projects. The first chapter is titled “How much does tuberculosis screening cost? A systematic review of economic evaluations among general population, children and close contacts” and represents a systematic review of the cost effectiveness of systematic screening in TB. This was initially commissioned by the World Health Organization (WHO) for their Guideline Development Group (GDG) meeting for TB screening. The second chapter is titled “How much does HIV self-testing cost? A systematic review of the economic literature” and is a systematic review around the economic evidence for self-testing for HIV. We then used the inputs extracted from the literature review of HIVST (chapter 2) to build an economic model to estimate the cost utility of HIVST (chapter three). This systematic review and model (chapter two & chapter three) were commissioned by the Foundation for Innovative New Diagnostics (FIND).

Chapter One: Systematic screening for Tuberculosis

Tuberculosis (TB) remains a significant contributor to morbidity and mortality worldwide and is the leading cause of infectious death globally[34]. Tuberculosis is an airborne infectious disease caused by Mycobacterium tuberculosis, that can manifest as pulmonary and/or extrapulmonary disease.

Tuberculosis is transmitted by airborne particles expelled by an infected individual upon coughing or sneezing[35]. The reproductive capacity of tuberculosis has been estimated to be between 3-5, depending on population factors[36, 37]. The reproductive capacity of tuberculosis increases with population density and proportion of "high risk" individuals within a community[38]. This helps to explain why the burden of tuberculosis is heavily skewed towards vulnerable and marginalized populations within Canada and worldwide. The World Health Organization (WHO) reported that in 2019 there were 1.4 million TB- related deaths and 10 million new infections[7].

The WHO developed a global tuberculosis strategy in 2000 (End TB), developing strategies for preventing and treating tuberculosis and targets for progress. In September 2018, all members of the United Nations (UN) met to address tuberculosis on a global level. This led to a reaffirmation of the WHO's End TB Strategy and commitment to the Sustainable Development Goals (SDGs)[11]. The most recent iteration of SDGs were agreed upon by United Nations members in 2015 and provide an outline of seventeen priorities for global development. The SDGs and End TB Strategy set outtargets, with the ultimate goal of ending the tuberculosis epidemic by 2030. Follow-up surveillance in 2019, showed a cumulative global reduction in TB incidence of 6.3% between 2015-2018, nowhere near the goal of a 20% reduction set out by the End TB Strategy for 2015-2020. There were large geographic disparities noted, with a disproportionate burden of TB related morbidity and mortality focused in low- and middle-

income countries (LMIC). Currently, eight countries (in Africa and South East Asia) account for over 66% of tuberculosis cases world-wide[34].

One of the strategies to reduce the global burden of tuberculosis has been the implementation of systematic screening programs within communities. Historically, passive case finding (PCF) has been the standard for tuberculosis diagnosis and treatment[20]. Passive case finding is when an individual develops symptoms and self-presents to a health care facility for diagnosis and treatment. The key principle of systematic screening is that individuals are screened before self-presenting to the health care system with symptoms of active disease. This decreases the period in which individuals can transmit tuberculosis to others since they are screened for disease earlier which should theoretically decrease the transmission and incidence and improve treatment outcomes among a community[39]. The individual programmatic components of systematic screening are variable, with many different methods for screening individuals. Systematic screening programs may involve door-to-door symptom screening of the community or targeted testing of asymptomatic, high-risk subpopulations[27]. The algorithms used for systematic screening can involve a variety of different diagnostic tools including symptom screening, chest X-ray, computer automatic detection (CAD) of X-ray films, Xpert MTB/RIF assay, detection of mycobacterial lipoarabinomannan (LAM) antigen in urine, sputum smear or microscopy and serum markers of inflammation. The yield of systematic screening is dependent on both program and population factors.

For example, the success of systematic screening depends on the underlying prevalence of tuberculosis within a population (the pretest probability of detecting tuberculosis). The generalizability of one systematic screening strategy to another community cannot be assumed due to variations in population preferences, underlying health system structure, TB prevalence and associated costs.[40].

As countries move towards reaching end TB targets, diagnosing all cases appropriately and in a timely manner is critical. As systematic screening becomes integrated into the global strategy to combat tuberculosis, it is imperative for economic evaluations to be conducted to ensure that limited resources are wisely used. Systematic screening programs can incur large costs[41], especially given that high risk groupsfor tuberculosis are often marginalized or in remote regions[42]. The costs incurred by systematic screening programs include costs of organizing and implementing the screening activity but also subsequent diagnostic follow-up and treatment costs. The benefits of systematic screening would be earlier detection of tuberculosis and decreased long-term morbidity and mortality. On a population level, increased detection and treatment of active tuberculosis should lead to reduced transmission and decreasingtuberculosis prevalence within a community over time.

The first chapter of my thesis represents a systematic review of the economic literature around systematic screening for active tuberculosis. This article has been accepted for publication to the International Journal of Tuberculosis and Lung Disease and is expected to be published in January 2021. This manuscript reviews the existing literature for the systematic screening among the general population, close contacts of individuals with TB and children. This systematic review was initially commissioned and presented to the WHO for their GDG in September 2020. We have published the data for people living with HIV (PLHIV) in a separate manuscript that has been accepted for publication in BioMed Central Infectious Disease (BMCID).

How much does tuberculosis screening cost? A systematic review of economic evaluations among general population, children and close contacts

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Abstract

Background:

Active case finding (ACF) for tuberculosis has been recommended as a method to address tuberculosis ona global level, however involves significant costs and health system burden.

Methods:

We conducted a systematic review of the existing economic literature on ACF for tuberculosis to summarize the costs, cost-effectiveness and affordability and key factors that influence costs and cost- effectiveness. Specific populations of interest included the general population, children and close contacts (CC).

Results:

We identified 21 studies that provided both cost and outcome data on screening for TB among thepopulations of interest. All were from low- and middle-income settings.

Studies were heterogenous in the intervention, included costs and reported outcomes. The incremental cost-effectiveness ratio (ICER) estimates ranged from $281-$698 per disability adjusted life year (DALY)averted among the general population, $619 per DALY averted among children and $372-$3718 per DALY averted among CC.

Conclusion:

Prevalence of TB among targeted high-risk groups was consistently identified across a majority of studies as a driver of cost-effectiveness. The heterogeneity of the included costs and outcomes across the economic literature for ACF suggests a need for standardization of included cost components and key economic evaluation methods to improve comparability and generalizability of results.

Background

Tuberculosis (TB) remains a major contributor to global morbidity and mortality, with a disproportionate burden of disease in low- and middle-income settings. To achieve global TB reductiontargets, a multipronged approach is needed including primary prevention, early detection, and effective treatment. Active case finding (ACF) is a component of the End TB strategy launched by the World Health Organization (WHO)[1] and has been proposed to reduce TB burden within endemic and high risk communities. ACF can incur large costs[2], especially given that groups at high risk for TB are often marginalized or in hard to reach regions[3]. It is imperative that economic evaluations of screening approaches are considered to ensure limited resources are used wisely.

To inform the WHO's Guideline Development Group (WHO GDG) meeting held in 2020 to update the guidance on ACF for active TB[4, 5], we performed a systematic review of published literature on economic evaluations for TB screening focusing on the general population, children and close contacts (CC). Findings for people living with HIV (PLHIV) and those with clinical and structural risk factors are published in a separate manuscript. Historically, passive case finding (PCF) has been the standard of care for TB diagnosis and treatment[6], wherein an individual develops symptoms and presents to the health system to be diagnosed and treated. A major component of ACF is that individuals are screened before presenting to the health care system, with the aim of diagnosis occurring earlier in their disease progression, thereby reducing the time people transmit to others and improving treatment outcomes for individuals with TB. While screening requires an investment of resources, it is hypothesized that earlier diagnosis and treatment leads to improved patient outcomes, including reduced mortality, decreased TB transmission and subsequent lower community incidence[7, 8].

Screening and diagnostic tools range from simple options, such as the WHO 4 symptom screen

(4SS), to more technically complex tools including sputum smear microscopy, chest radiography, and molecular assays (i.e., Xpert MTB/RIF); each with their own discrete costs and effectiveness profiles. Detailed understanding of screening program costs and cost-effectiveness, including key parameters and conditions to ensure cost-effectiveness across different settings will be critical for TB programs in scaling up ACF for TB.

We conducted a review to summarize the existing literature on economic evaluations of screeningfor active pulmonary TB and identify drivers of cost-effectiveness for ACF of TB. To our knowledge, this is the first study to summarize the economic literature for ACF in TB among these subpopulations.

Methods

A search strategy was developed including key terms for active TB, ACF and economic evaluations and is included in the appendices. The search was performed in three databases: Embase, OVID and Scopusfrom January 1, 2010-November 30, 2020.

Studies were included if screening targeted active pulmonary TB disease; studies with exclusively extrapulmonary or latent TB infection were excluded. For studies to have been considered an economicevaluation, data about costs and a health outcome must have been reported. This included modeling studies where inputs from previous literature were used within an economic model to predict the cost- effectiveness of screening. Study selection followed PRISMA guidelines.

Abstracts were screened by two independent screeners (BE, HA) with conflicts resolved by a third reviewer (AZ). Full text reviews were completed, and data was extracted from eligible studies (BE, HA).The CHEERS checklist[9], a quality assessment tool specifically designed for economic evaluations, was completed for all studies. Costs were converted back into their

original currency, adjusted for inflation[10] and converted back into USD 2020.

Given the underlying heterogeneity of the included economic studies, meta-analysis was not conducted.Included studies are summarized in a narrative format, stratified by subpopulation of interest and screening algorithm. This was a systematic review and ethics approval was not required.

Results

Study characteristics

Characteristics of the twenty-one included studies are summarized in tables 1-3, by population of interest.Identified studies include both experimental studies (11/21), where an intervention was implemented, and modeling based economic studies (9/21), using decision tree analysis, dynamic transmission modeling and/or Markov models. One study included both an empiric intervention and a component of economic modeling[11].

Subpopulations

Active Case Finding in the General Population

Thirteen studies assessed the impact of ACF in the general population, with 92% (12/13) taking place in settings with a high prevalence of TB (>1%) among the general population. The studies included both empiric studies which collected primary cost data (7/13) and modeling studies which predicted cost- effectiveness (6/13).

The empiric studies reported cost estimates ranging from $47-$1,871 per case diagnosed, while the modeling studies used heterogenous outcomes including DALYs averted, QALYs gained and cost percase diagnosed.

Using willingness to pay thresholds (WTP) to determine cost-effectiveness, 84% of studies (11/13), found screening was cost-effective in the general population. Cost-effectiveness

estimates ranged from a cost savings of $18 per case detected[11] in Pakistan using clinic based screening to $1,871 per case detected for a mobile screening unit that included downstream treatment costs in Uganda[12]. Despite similar screening algorithms, studies across different countries resulted in variable average cost-effectiveness estimates. Jo et al. reported the cost-effectiveness of door-to-door screening followed by Xpert on a sputum sample to be $375 per case detected in Tajikistan[13]. A similar screening algorithm was modeled by Nishikiori et al.[14] and predicted to cost $550 per case detected. Despite a similar underlying prevalence of TB, the unit costs for the individual diagnostic tests were higher in the Nishikiori study which led to an increased cost compared to the Jo study.

Among the general population, screening and diagnostic algorithms shown to be cost-effective used 4SS, followed by additional tests for those who had symptoms. Using screening chest X-ray (CXR) in individuals regardless of symptoms was assessed by two studies with differing results. Bogdanova et al. found that upfront CXR was only cost-effective among high-risk subgroups (PLHIV, prisoners, homeless) and not among the general population or children[15], where it was associated with a mean cost of $13,242 per case diagnosed.

Machekera et al.[16] also costed screening CXR in Zimbabwe and found that the cost was $190 per case additional case diagnosed compared to PCF. Upfront CXR was cheaper but less effective than a symptom screen followed by CXR among the general population. The higher underlying prevalence of TB in Zimbabwe (1.8% compared to 0.6% in Russia) may contribute to the differing cost-effectiveness estimates.

Murray et al. modeled the cost-effectiveness of CXR or C-reactive protein (CRP) as the initial screeningtest in individuals with prolonged cough presenting to a healthcare facility[17]. They found that this was cost-effective, with an ICER of $643-$669 per year life gained (YLG), when the population TB prevalence was 5% or higher. Within populations with a lower TB

prevalence, the intervention was only cost-effective when the unit cost of the CXR/CRP could be lowered to $3 from $4-$6 USD.

Hinderaker et al reviewed 51 different TB programs across 18 countries, with differing components and outcomes. They found that among programs including ACF, the cost per case diagnosed ranged from $77-$2,153.

Active Case Finding in Children

Three studies assessed the economic impact of ACF in children; one from Pakistan was performed exclusively in children while two from Myanmar and Uganda stratified results for children. Htet et al. in Myanmar modeled cost-effectiveness of screening children who were CC of individuals with TB through symptom screen followed by diagnostic CXR, sputum smear and Xpert. They found the cost per case detected ranged from $14-$19 in children under 15 years of age[18]. A study based in Pakistan, implemented a symptom screen of children presenting to pediatric medical clinics and referred those with positive screens to a tertiary care center. The cost-effectiveness of a symptom screen within clinics was estimated to range from $31-$46 per case detected[19]. Mupere et al. used a decision tree model to predict the cost-effectiveness of ACF by door-to-door symptom questionnaires in Uganda. In the 10-14 year old age range, the intervention was cost-effective, at an ICER $619 per quality adjusted life year (QALY) gained compared to PCF[20].

Active Case Finding in Close Contacts

Eleven studies assessed the impact of ACF among CC (neighbours and household members of TB cases) including both interventional studies (n=6) and economic modeling (n=5). Study characteristics are summarized in table four. All studies concluded that screening among CC was cost-effective. The interventional studies reported costs ranging from $38-$2,843 per case

identified, while modeling studies estimated cost per case identified from $38-$520 per case identified and $372-$3,659 per DALY averted.

Many of the ACF interventions among CC included symptom screening as the initial test but the upfront screen included a variety of other diagnostics, including Xpert, CXR and sputum screen. Htet et al. modeled the cost-effectiveness of upfront CXR among CC, compared to a symptom screen followed by further diagnosed testing. They found that using upfront CXR was more sensitive and associated with anadditional cost of $38 per case diagnosed. In contrast to the findings among the general population, screening by upfront CXR[18, 21] and Xpert[22] were found to be cost-effective among CC of individuals withTB. Shah et al. used decision analysis to model the cost-effectiveness of Xpert in CC in Peru, regardless of symptoms, and estimated an ICER of $ 3,659 per DALY averted which was considered cost-effective by the authors

Drivers of Cost Effectiveness

Factors that impacted cost effectiveness were reported in both empiric and modeling studies. Within the modeling studies, they were varied in sensitivity analyses and those that impacted the cost effectiveness ICER beyond the willingness to pay threshold were reported as significant. The most frequently reported drivers of cost effectiveness were programmatic costs of the screening intervention and underlying prevalence of TB. The drivers of cost effectiveness are summarized stratified by empiric and modeling studies in table five.

Discussion

Summarizing the cost-effectiveness of ACF across studies is challenging, as cost-effectiveness is population specific and thus generalizing to different contexts may not be appropriate. There was no standardized screening intervention or outcome reporting between studies. The costs included among the studies also varied, with some including upfront screening costs while others included

lifetime treatment costs. Programmatic and infrastructure costs were underreported, yet when included were found to impactcost-effectiveness.

Heterogeneity in costs included between economic evaluations suggests a need for standardized costing and outcome measures. A recent literature review identified 31 different guidelines for economic evaluation, with a lack of consensus across recommendations[23]. Standardization of these guidelines wouldhelp to improve the generalizability of economic evaluations.

Most studies reported outcomes as a cost per case diagnosed. Utility measures such as QALYs or DALYswere included in 33% (7/21) of the economic evaluations. Utility measures provide more information than cost per case, which does not account for quality of life or mortality impact. Additionally, utility measures allow for comparisons between settings and interventions. Future economic evaluations should ensure that at least one utility measure is considered beyond cases detected.

There was one study that used a transmission model to assess the potential impact of ACF on TB incidence over time[24]. Increasing rates of treated TB led to reductions in underlying prevalence and incidence of TB over time and ACF was highly cost-effective in all three included countries. Screening campaigns that were longer in duration (over three years) had more significant impact on community TBprevalence and were increasingly cost-effective.

Studies among children were underrepresented, and when reported were included as a subgroup analysis with small numbers. Only one study among children reported utility measures, [20] and did not model costutility in children under ten years of age, which limits the generalizability to the broader pediatric population. Younger children have higher rates of viral respiratory tract infections that may lead to false positives on symptom screening and are typically not able to provide sputum for testing[25]. Higher false positive rates have the potential to lead to more costly

downstream diagnostics, and higher ICERs.

All studies among CC found that ACF was cost-effective. These included studies that used CXR and Xpert as screening tools among individuals who were asymptomatic, which differed from the general population where these tests were typically cost-effective only among those who were symptomatic. Close contacts had higher case detection rates, likely due to the increased prevalence of TB among this group. No studies included preventative treatment of CC, which may increase both the cost and efficacy of interventions. ACF was cost-effective both in the general population when initiated through symptom screening and in high-risk populations, but it is important to note cost-effectiveness was determined using willingness to pay (WTP) thresholds chosen by study authors.

As expected, the vast majority (20/21) of studies found that ACF was associated with additional costs, although Hussain et al actually predicted that ACF was less costly than PCF when implemented in Pakistan[11]. Whether the studies concluded that ACF was cost-effective, depended on whether the additional cost incurred was less than the WTP threshold. Most studies did explicitly state the WTP, however the methodology of determining WTP varied between studies. The most common WTP threshold was based on the country gross domestic product (GDP) per capita, with interventions thatcosted less than the GDP per capita per DALY averted being cost-effective.

Limitations

There was significant heterogeneity within the included studies in terms of reference strategy, costs included, and outcome used which led to the narrative summary of our results rather than a meta-analysis. Cost-effectiveness evolves over time, which is why we limited our search strategy to publications within the past twenty years. It is still likely that the earlier studies

include outdated cost estimates.

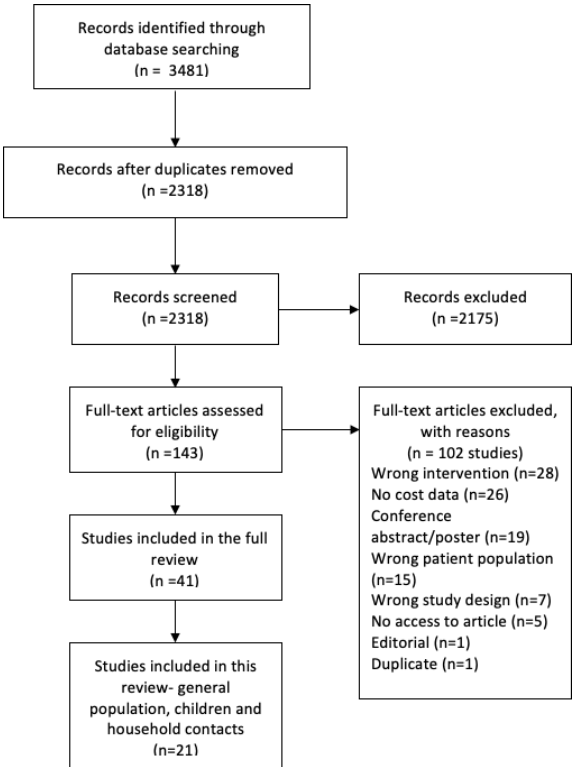
This systematic review was restricted to published literature, and it is likely that there is a publication bias where programs that are not cost-effective are less likely to be published. There were only three studies included, where ACF was not considered to be cost-effective in at least one of the included scenarios[15, 17, 26].

Conclusion

This is the first report that summarizes the existing economic evidence for ACF for active TB among keysubpopulations. There were a large number of included studies in this systematic review which representsa diverse group of interventions and study locations. The heterogeneity across the economic literature forACF suggests a need for standardization of included components to improve generalizability of results.

As the COVID-19 pandemic has continued, TB notifications have decreased[27] and on a global level we risk losing progress on our effort to control TB. This makes ACF for TB all the more important given the competing priorities that health care systems face and the increasing reluctance of individuals to access medical care due to the risk of COVID-19 exposure[28]. With many competing priorities among global health care systems, understanding the cost-effectiveness of ACF among different subpopulations is an essential component to mitigating TB-related morbidity and mortality.

Figure One: Prisma Diagram



The full review was presented at the WHO GDG in 2020. There are twenty studies on ACF for

TB amongPLHIV that have been submitted for publication in a separate manuscript.

Appendix One: Search Strategy

(tb or tuberculosis).mp OR Latent Tuberculosis/ or Extensively Drug-Resistant Tuberculosis/ or Tuberculosis/ or Mycobacterium tuberculosis/ or Tuberculosis, Pulmonary/ or Mycobacterium/ or Tb/

AND ((active adj3 case finding) or intens*adj 3 case finding).mp. OR (tuberculosis adj3 case finding).mp.OR mass screening/ or mass CXR/ or multiphasic screening/

AND (cost-benefit or cost or economic or cost-effectiveness or cost-utility or disability adjusted life year or DALY or quality-adjusted life year or QALY or cost benefit analysis or cost-effectiveness analysis orquality of life or utility).mp

Table 1: Summary of Study Results Stratified by Outcome Measure

Studies (N)	Location	Active Case Finding Algorithms used (initial screen)	Outcome (USD, 2020)
General Population			
N=9	Democratic Republic of the Congo, India, Cambodia, South Africa, Zimbabwe Russia, Sub-Saharan Africa, Pakistan	Door to door screening for prolonged cough, symptom screen, symptom screen and CXR, CXR, Xpert	$47-$1871 / case detected
N=2	South Africa, China & India, Pakistan	Symptom screen	$281-$698 / DALY averted
N=1	Uganda	Symptom screen	$125 / QALY gained
N=1	Uganda	Prolonged cough followed by CXR or CRP	$643-$669 / years of life gained
Children			
N=2	Pakistan, Myanmar	Symptom screen, CXR	$19-$46 / case detected
N=1	Uganda	Symptom screen	$619 / QALY
Close Contacts			
N=8	Cambodia, Myanmar, DRC, Russia, Zimbabwe, Myanmar	CXR, symptom screen, symptom screen and CXR	$38-$2843 / case detected
N=3	Cambodia, Vietnam, Peru	CXR	$372-$3,659 / DALY averted

This table summarizes the included study results, stratified by subpopulation of interest with grouped outcome measures.

Abbreviations: CXR, chest X-ray; Xpert, Gene Xpert; DALY, disability adjusted life year; QALY,quality adjusted life year

Table 2: Studies Among the General Population

Study, Year	Country setting	Study population	Study Type	Screening interventions and diagnostic tools	Costing Elements	Reference screening strategies and diagnostic tools	Analysis perspective	Willingness to Pay Threshold
Andre, 2018	Democratic Republic of the Congo	General population	Empiric	Volunteer screeners went door to door and referred those with prolonged cough to specialty clinics	Diagnostic costs	PCF	Health system	Not stated
Azman, 2014	South Africa, India, China	General population	Model (including transmission model)	Estimated impact of discrete ACF campaigns of varying lengths	Diagnostic and treatment costs	PCF (historical data based on pre-intervention case rates)	Health system	Cost per DALY averted < GDP per capita
Bogdanova, 2019	Russian Federation	General population, PLHIV, homeless, migrants, chronic medical conditions	Empiric	1) Contact tracing done then CXR and SSM for diagnosis; 2) Mass screening in hospitals	Diagnostic costs including travel	PCF including CXR and SSM	Health system	Not stated

				using CXR and SSM; 3) Mass screening in TB dispensary using mobile CXR then SSM				
Daftary, 2019	India	General population	Empiric	Pharmacist incentives provided for symptom screening then referral for CXR or specialized clinic if positive	Programmatic costs including provider incentive (full diagnostic costs and treatment costs not included)	Referrals through pharmacy prior to establishing incentives	Health system	Cost per case detected < $1000
Hinderaker, 2011	18 countries	General population	Empiric	FIDELIS ACF programs with varying programmatic elements	Multiple interventions included	PCF	Health system	Program specific
Hussain, 2019	Karachi, Pakistan	General population accessing outpatient clinics	Empiric and modeling	Symptom screen followed by CXR, Xpert and sputum smear	Diagnostic and treatment costs modeled	PCF	Health system & Patient incurred	Cost per DALY averted < GDP per capita
Jo, 2020	Cambodia, Tajikistan	Cambodia – General population	Empiric	Door to door symptom screen, if	Diagnostic costs	N/A	Health system	Not stated

		in rural areas Tajikistan – detention centers and diabetic patients		positive patients had mobile CXR and Xpert				
Kranzer, 2012	South Africa	Peri-urban population attending mobile testing	Empiric	Mobile HIV testing van added TB testing: WHO 4SS for all HIV-, if symptomatic then SSM; all PLHIV referred to TB clinic	Diagnostic and treatment costs	N/A	Health system	Cost per DALY averted < GDP per capita
Machekera, 2019	Zimbabwe	General population; substratified into high-risk subgroups	Model	4SS and CXR if either 4SS or CXR positive then Xpert	Diagnostic costs	WHO algorithms: 1)4SS, if positive then Xpert 2) 4SS, if positive then CXR, then Xpert 3) CXR, then Xpert	Health system	Not stated
Mupere, 2013	Uganda	General population	Model	Door to door volunteer led	Diagnostic and treatment costs	PCF	Health system	Cost per DALY averted <

				symptom screening				GDP per capita
Murray, 2016	Uganda	General population	Model	SS with prolonged cough, if positive then CXR or CRP then Xpert for diagnosis	Diagnostic and treatment costs	PCF	Health system	Cost per DALY averted < GDP per capita
Nishikiori, 2013	N/A	General population	Model	Generic ACF program	Diagnostic costs (excluded programmatic costs)	PCF	Health system	Cost per case detected <$200
Sekandi, 2015	Uganda	CC, urban population	Model	1) PCF + ACF- door to door screening for chronic cough, if positive then SSM 2) PCF + CC investigations: 4SS and SS or CXR in CC	Diagnostic costs	PCF	Health system & patient incurred	Cost per DALY averted < GDP per capita

Abbreviations: CXR, CXR; Xpert, Gene Xpert; DALY, disability adjusted life year; QALY, quality adjusted life year; CC, close contacts; WHO4SS, World Health Organization four symptom screen; HCW, health care workers; PCF, passive case finding; SSM, sputum smear and microscopy; CRP, C-reactive protein; PLHIV, people living with human immunodeficiency virus; CHW, community health care workers.

Table 3: Studies Among Children

Study, Year	Country setting	Study population	Study Type	Screening interventions and diagnostic tools	Costing Elements	Reference screening strategies and diagnostic tools	Analysis perspective	Willingness to Pay Threshold
Htet, 2017	Myanmar	CC- results stratified by age	Model	4SS followed by SSM and then CXR	Diagnostic costs	Symptom screen then CXR	Health system	Not stated
Malik, 2019	Pakistan	Children	Empiric	Incentives for symptom screening in outpatient clinics	Diagnostic costs	Historical data prior to incentive program	Health system	Not stated
Mupere, 2013	Uganda	General population	Model	Door to door volunteer led symptom screening	Diagnostic and treatment costs	PCF	Health system	Cost per DALY averted < GDP per capita

Abbreviations: CC, close contacts; CXR, chest X-ray; PCF, passive case finding.

Table 4: Studies among Close Contacts

Study, Year	Country setting	Study population	Study Type	Screening interventions and diagnostic tools	Costed Elements	Reference screening strategies and diagnostic tools	Analysis perspective	Willingness to Pay Threshold
Andre, 2018	Democratic Republic	General population	Empiric	Volunteer screeners	Diagnostic costs	PCF	Health system	Not stated

	of the Congo			went door to door and referred those with prolonged cough to specialty clinics				
Bogdanova, 2019	Russian Federation	General population, PLHIV, homeless, migrants, chronic medical conditions	Empiric	1) Contact tracing done then CXR and SSM for diagnosis; 2) Mass screening in hospitals using CXR and SSM; 3) Mass screening in TB dispensary using mobile CXR then SSM	Diagnostic costs including travel	PCF including CXR and SSM	Health system	Not stated
Eang, 2012	Cambodia	Rural residents, targeted low-income areas	Empiric	Upfront CXR in CC and close neighbours with symptoms	Diagnostic costs	N/A	Health system	Not stated
Htet, 2017	Myanmar	CC- results stratified by age	Model	WHO 4SS followed by	Diagnostic costs	Symptom screen then CXR	Health system	Not stated

				SSM and then CXR				
James, 2017	Cambodia	Poor, urban residents; elderly living in rural areas	Empiric	1) Door-to-door screening WHO 4SS, symptomatic patients SSM, then Xpert and culture; 2) Door-to-door screening older patients WHO 4SS, if symptomatic referred for CXR screening, if positive then Xpert	Diagnostic costs	Compared ACF programs	Health system	Not stated
Lung, 2019	Vietnam	CC	Empiric	Upfront CXR, followed by symptom screen and sputum smear	Diagnostic and treatment costs	PCF	Health care system	Cost per DALY averted < 3x GDP per capita
Machekera, 2019	Zimbabwe	General population; substratified into high-risk subgroups	Model	4SS and CXR if either 4SS or CXR positive then Xpert	Diagnostic costs	WHO algorithms: 1)4SS, if positive then Xpert 2) 4SS, if positive	Health system	Not stated

						then CXR, then Xpert 3) CXR, then Xpert		
Myint, 2019	Myanmar	CC	Empiric	Second (enhanced) CC with CXR and sputum smear of all contacts	Diagnostic costs	Routine screening-symptom screening of all CC	Health care system	Cost per case < GDP per capita
Sekandi, 2015	Uganda	CC, urban population	Model	1) PCF + ACF- door to door screening for chronic cough, if positive then SSM 2) PCF + CC investigations: 4SS and SS or CXR in CC	Diagnostic costs	PCF	Health system & patient incurred	Cost per DALY averted < GDP per capita
Shah, 2017	Peru	CC	Model	1) PCF + CC investigation using WHO 4SS and SSM; 2) PCF + upfront Xpert; 3) HCW visits to screen CC using WHO	Diagnostic and treatment costs	PCF	Health system	Cost per DALY averted < GDP per capita

				4SS and if positive Xpert				
Yadav, 2014	Cambodia	CC	Model	CC underwent CXR and symptom screening regardless of symptoms. Neighbours with symptoms underwent CXR and further work up.	Diagnostic and treatment costs	PCF	Health system	Cost per DALY averted < GDP per capita

Table 5: Drivers of Cost Effectiveness of Active Finding for TB

Empiric Studies		
Driver of Cost Effectiveness	**Direction of Impact**	**Included Studies**
Programmatic costs (including implementation, transport and personnel)	Increased programmatic costs increase cost per case diagnosed	Lung, 2019; Kranzer, 2012
Access to health care	Decreased access of health care in the targeted population decreased cost per case diagnosed	Andre, 2018
TB Prevalence	Increased TB prevalence in the targeted population decreased cost per case diagnosed	Bogdonova, 2019
Unit costs of diagnostic tests (i.e., Xpert, SSM, CXR)	Increased unit costs of diagnostic tests increased cost per case diagnosed	Jo, 2020
Modeling Studies		
Driver of Cost Effectiveness	**Direction of Impact**	**Included Studies**
TB Prevalence	Increased TB prevalence in the targeted population decreased cost per case diagnosed	Azman, 2014; Mupere, 2013; Machekera, 2019; Murray, 2016; Nishikiori, 2013; Sekandi, 2015; Shah, 2017; Yadav, 2014
Programmatic costs (including implementation, transport and personnel)	Increased programmatic costs increased cost per case diagnosed	Azman, 2014; Mupere, 2013; Nishikiori, 2013; Sekandi, 2015; Shah 2017; Yadav, 2014
Mortality of untreated TB	Increased mortality of untreated TB decreased cost per case diagnosed	Murray, 2016; Yadav, 2014
Morbidity of treated TB	Increased morbidity of treated TB increased cost per case diagnosed	Shah, 2017; Yadav, 2014
Uptake of facility-based testing	Increased uptake of facility-based testing	Murray, 2016; Hussain, 2019

	increased cost per case diagnosed	
ACF campaign duration	Increased duration of the intervention decreased cost per case diagnosed	Azman, 2014
Age	Increased age in the targeted population decreased cost per case diagnosed	Mupere, 2013
Loss to Follow Up	Increased loss to follow up during TB treatment increased cost per case diagnosed	Shah, 2017

References

1. World Health Organization. The End TB Strategy. 2014.
2. Sawert H, Kongsin S, Payanandana V, Akarasewi P, Nunn PP, Raviglione MC. Costs and benefits of improving tuberculosis control: the case of Thailand. Soc Sci Med. 1997;44: 1805-1816.
3. Jit M, Stagg HR, Aldridge RW, et al. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ. 2011;343: d5376.
4. World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Systematic Screening forTuberculosis Disease. March 2021. .
5. World Health Organization. Systematic screening for active tuberculosis: principles andrecommendations2013.
6. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005;9: 1183-1203.
7. Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet. 2010;376: 1244-1253.
8. Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. Int J Tuberc Lung Dis. 2013;17: 432-446.
9. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Int J Technol Assess Health Care. 2013;29: 117-122.
10. Bank W. Inflation, consumer prices %, 2020.
11. Hussain H, Mori AT, Khan AJ, et al. The cost-effectiveness of incentive-based active case finding for tuberculosis (TB) control in the private sector Karachi, Pakistan. BMC health services research. 2019;19: 690.
12. Hinderaker SG, Rusen ID, Chiang CY, Yan L, Heldal E, Enarson DA. The FIDELIS initiative: innovative strategies for increased case finding. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15: 71-76.
13. Jo Y, Mirzoeva F, Chry M, et al. Standardized framework for evaluating costs of active case-finding programs: An analysis of two programs in Cambodia and Tajikistan. PLoS One. 2020;15: e0228216.
14. Nishikiori N, Van Weezenbeek C. Target prioritization and strategy selection for active case-finding of pulmonary tuberculosis: a tool to support country-level project planning. BMC public health. 2013;13: 97.
15. Bogdanova E, Mariandyshev O, Hinderaker SG, et al. Mass screening for active case finding of pulmonary tuberculosis in the Russian Federation: how to save costs. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2019;23: 830-837.
16. Machekera SM, Wilkinson E, Hinderaker SG, et al. A comparison of the yield and relative cost of active tuberculosis case-finding algorithms in Zimbabwe. Public health action. 2019;9: 63-68.

17. Murray M, Cattamanchi A, Denkinger C, Van't Hoog A, Pai M, Dowdy D. Cost-effectiveness of triage testing for facility-based systematic screening of tuberculosis among Ugandan adults. BMJ global health. 2016;1: e000064.
18. Htet KKK, Liabsuetrakul T, Thein S. Cost-effectiveness of a new strategy to detect pulmonary tuberculosis in household contacts in Myanmar. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2017;21: 181-187.
19. Malik AA, Hussain H, Creswell J, et al. The Impact of Funding on Childhood TB Case Detection in Pakistan. Tropical medicine and infectious disease. 2019;4.
20. Mupere E, Schiltz NK, Mulogo E, Katamba A, Nabbuye-Sekandi J, Singer ME. Effectiveness of active case-finding strategies in tuberculosis control in Kampala, Uganda. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17: 207-213.
21. Myint O, Sriplung H, San CC, Chongsuvivatwong V. Additional active tuberculosis cases detected and costs incurred by a second household contact investigation. Public Health Action. 2019;9: 182-185.
22. Shah L, Rojas M, Mori O, et al. Cost-effectiveness of active case-finding of household contacts of pulmonary tuberculosis patients in a low HIV, tuberculosis-endemic urban area of Lima, Peru. Epidemiology and infection. 2017;145: 1107-1117.
23. Sharma D, Aggarwal AK, Downey LE, Prinja S. National Healthcare Economic Evaluation Guidelines: A Cross-Country Comparison. Pharmacoecon Open. 2021.
24. Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and Indi. BMC Medicine. 2014;12: 216.
25. Zar HJ, Connell TG, Nicol M. Diagnosis of pulmonary tuberculosis in children: new advances. Expert Rev Anti Infect Ther. 2010;8: 277-288.
26. Sekandi JN, Dobbin K, Oloya J, Okwera A, Whalen CC, Corso PS. Cost-effectiveness analysis of community active case finding and household contact investigation for tuberculosis case detection in urban Africa. PLoS One. 2015;10: e0117009.
27. Kwak N, Hwang SS, Yim JJ. Effect of COVID-19 on Tuberculosis Notification, South Korea. Emerg Infect Dis. 2020;26: 2506-2508.
28. Czeisler ME, Marynak K, Clarke KEN, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. MMWR Morb Mortal Wkly Rep. 2020;69: 1250-1257.

Chapter Two: HIV Self-Testing; A Systematic Review of the Current Economic Literature

Our literature review suggested that systematic screening for TB can be cost effective especially when undertaken among high-risk subpopulations. HIV represents another infectious disease that is a major cause of morbidity and mortality on a global level. The United Nations General Assembly, laid out the 95/95/95 targets for HIV diagnosis and care to be met by the end of 2020[43]. Many countries have made progress on controlling the transmission HIV, but there remains a disproportionate HIV related burden on low- and middle-income countries. Additionally, certain subpopulations such as men who have sex with men (MSM), sex workers and intravenous drug users (IVDU) have much higher rates of diagnosed and undiagnosed HIV compared to the general population. These subgroups may also face barriers to accessing conventional health care which can delay diagnosis and treatment. It is estimated that globally there are approximately 6 million PLHIV who remains undiagnosed. Lack of diagnosis means that PLHIV do not receive appropriate therapy and have increased risk of progressing to AIDS. Additionally, individuals who are not receiving anti-retroviral therapy (ART) have an increased risk of transmitting HIV[12, 42].

HIV self-testing (HIVST) represents an innovative new method of diagnosing HIV that may be more accessible to traditionally marginalized or remote subpopulations. However, there is a paucity of literature around cost and cost-effectiveness of HIVST. We have conducted a systematic review to assess the cost and cost-effectiveness if HIVST across various settings, this review was then used to develop and parametrize an economic model to assess the cost utility of HIVST (chapter three). This systematic review looked at the current economic evidence for HIVST among low- and middle-income settings.

Both the systematic review and model were commissioned and financially supported by the Foundationfor Innovative New Diagnostics (FIND). The findings from this systematic review

will be presented to FIND and this manuscript will be submitted for publication.

How much does HIV self-testing cost? A systematic review of the economic literature

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Background

HIV self-testing (HIVST) has been proposed as an innovative approach to diagnose human immunodeficiency virus (HIV)[1]. HIVST allows an individual to collect their own specimen (via sputum or blood) and conduct/interpret the HIV test independently or with support from a health care worker, whether to be performed within the testee's home or in a healthcare facility. Individuals with positive self-tests would then have the ability to link to care and receive post-test counseling and confirmatory testing[2].

Previous literature has strongly suggested that HIVST is preferred by clients and has increased rates of uptake compared to conventional testing[3-7]. This has been shown among the general population, but also among conventionally hard to reach groups such as sex workers and truck drivers[8, 9]. HIVST can be linked with a variety of approaches, including community based and digital interventions, that can help support linkage to care[10].

HIVST offers a testing method that is acceptable to communities and empowers them to engage in their own health, rather than relying on a facility-based testing approach. As countries move towards achieving the 95-95-95 goal set out by UNAIDS[11], HIVST has been rapidly deployed among a broad range of contexts. Over sixty countries currently have HIVST guidelines or policies representing a spectrum of different health system contexts and endemic HIV rates[12].

While HIVST offers the potential to broaden accessibility of early HIV diagnosis and treatment initiation, this testing strategy incurs additional cost and requires linkage to confirmatory testing and treatment. On average, HIVST does have decreased rates of linkage to confirmatory testing and ART initiation[13].

Optimizing resource allocation is an important component of ensuring equitable health outcomes. While previous studies have suggested that HIVST can be cost effective[14, 15], this

represents the first systematic review to summarize the economic literature for HIVST. Our objective was to describe the current evidence for the cost effectiveness of HIVST within low- and middle-income countries.

Methods

A search strategy was developed including key terms for HIV, self-testing and costs. The search strategy is included in appendices.

The search was performed in two databases: Medline and Embase. Publications were included up until June 17, 2021. Bibliographies were further evaluated to search for additional eligible studies.

Studies were considered eligible if they assessed HIVST, included costs and were conducted in a low or middle income context as defined by the World Bank[16]. This included both modeling studies where inputs from previous literature were used within an economic model to predict the cost-effectiveness of screening and empiric studies where an intervention was conducted and cost data was collected. Studies were excluded if costs were not assessed or if studies were conducted in a high-income context. Study selection followed PRISMA guidelines[17].

Abstracts were screened by a single screener (AK). Eligibility of the full texts was confirmed by BE and AZ. Full text reviews were completed and data was extracted from eligible studies (BE, AK) utilizing a pre-piloted data abstraction form. Both individuals extracted data from all identified studies, and conflicts were resolved through a third party (AZ). Outcomes collected included the type of study (modeling/empiric), country, study population, HIVST approaches used, reference standard testing, as well as several economic-related outcomes whether they pertained to either HIVST or the standard of care (SOC) testing: the cost of HIVST kits, cost per case tested, cost per case diagnosed, cost per newly identified positive case, cost per

antiretroviral therapy (ART), average scale-up cost, drivers of testing costs, incremental cost-effectiveness ratio (ICER), cost per averted infection and cost per disability-adjusted life year (DALY) averted. Costs were converted back into their original currency, adjusted for inflation[18] and converted back and presented as USD 2020.

The results are sub-stratified by study type and summarized in narrative format. Given the underlying heterogeneity of the included studies, we did not feel that a meta-analysis of the data would be appropriate. As this was a systematic review, ethics approval was not required.

Results

Study Selection

As shown in Figure 1, the search strategy yielded 407 studies, of which 87 underwent full abstract review.Of these, 35 were excluded for various reasons: duplicate (n=13 publications), no outcomes of interest were identified (n=16) and the study was not conducted in a LMIC (n=7). As such, 51 full texts were reviewed:

36 full texts were excluded on the basis of: they did not include any outcomes of interest (n=22 publications), due to study design (n=8), as self-testing was not assessed (n=2), the full publication was unavailable (n=2), the evaluation of the study was in a high-income country (n=1) and one for being a conference poster (n=1). As such, a total of 15 publications comprised our final set.

The study characteristics and economic results among the included studies are reported in tables 1 and 2. Of these 15 eligible studies, 11 were empiric in nature meaning that an actual intervention was conducted and costing data was reported. The remaining four publications were modeling studies. A full description of the eligible publications is detailed below.

Empiric Studies

Bulterys et al. examined the costs of providing HIV self-test kits to pregnant women attending antenatal care living with HIV with the aim to increase testing to their male partners in Uganda. Three scenarios were evaluated: A- from the 'as-studied' perspective reflecting the research intervention, B- from a Ministry of Health (MOH) implementation perspective, and C- from a MOH roll-out perspective, representing the strategy used in Uganda to roll out HIVST distribution. Important distinctions to note in the MOH roll-out scenario include that counseling was provided in group sessions and that solely males with HIV positive results via HIVST underwent confirmatory testing, whereas individual counseling and universal confirmatory testing were part of scenarios A and B. In the 'as-studied' scenario where counseling was provided individually and research staff salaries were used in the calculation, self-testing costs were of $13.96 per female tested (regardless of HIV status), $11.89 per HIV-positive male and $10.55 per HIV- negative male. In the MOH implementation scenario using government health sector salaries, self-testing costs were of $9.45 per female self-tested, $7.87 per HIV-positive male and $6.99 per HIV-negative male.In the MOH roll-out perspective, self-testing costs were of $3.70 per female and $6.65 per HIV-positive male.

In a randomized controlled trial, Choko et al. evaluated the impact of an HIVST intervention aloneversus with additional interventions among pregnant women and their male partners in Malawi. While the standard of care (SOC) entailed a personalized invitation letter sent to male partners for HIV testing, five intervention arms were examined: in the first group, women were

provided with two HIVST kits for their partners; in the second group, two HIVST kits and phone call reminders were provided to participants' male partners; and in the remaining three groups, two HIVST kits were provided along with a variable conditional incentive ($3, $10 or a 10% chance of receiving $30 in a lottery). Costs per individual diagnosed with HIV ranged between $23.73-$28.08 depending on the financial incentive. Overall, the average ICER for HIVST was $127 per additional person who was started on antiretroviral therapy (ART).

In another RCT conducted in Malawi, Dovel and colleagues randomized participants in one of three groups:1- standard provider-initiated testing and counselling was provided; 2- optimized provider-initiated testing and counselling which additional provider training and morning HIV testing; and 3- facility-based HIVSTwhich provided a group demonstration and distribution of the usage of the Oraquick HIV self-test, private spaces for interpretation and counselling. The cost to test for HIV was highest in the HIVST group ($4.99), followed by the optimized provider-initiated group ($4.79) and standard provider-initiated group ($2.44). Cost for HIVST per new diagnosis and ART initiation were $189 and $279 respectively.

In a Kenyan costing analysis conducted by George et al., HIVST, whether performed in a clinic or at home,was promoted by short message service (SMS), among male truckers and female sex workers who irregularly tested for HIV. Cost per case diagnosed for HIVST was $10.13 compared to $5.01 for facility-based testing.

In Lesotho, D'Elbée and colleagues assessed the costs of adding HIVST to existing community-based HIV testing services. When only community-based HIV testing was available, the cost per case tested was $32.2. When both community-based testing and HIVST were available, the cost of the former was higher ($25.0)than HIVST ($15.4). They further observed that costs for HIV community-based testing was higher ($34.3)than HIVST when individual booths were offered ($14.0). In regard to the diagnosis of cases, costs were highest when HIVST was offered

($1,249) than when only conventional community-based testing ($956) and HIVST using individual booths was offered ($813).

Indravudh et al. examined the costs of community-led delivery of HIVST in Malawi. This intervention involved widespread delivery of HIVST kits to houses, along with community worker support for linkage to care. The cost per case diagnosed was on average $241, although this included previously diagnosed individuals. The average cost per case for the identification of a new HIV case, was $602.

Also in Malawi, in an evaluation of the general population aged over 18 years who reside in urban suburbs, Maheswaran and colleagues compared the testing approach of combining HIVST performed at home and facility-based testing to the standard of care (facility-based testing). While the average HIVST cost ($8.78) was similar to the health provider facility-based testing cost ($7.53-$10.57), the cost to diagnose a case of HIV was higher among the HIVST group ($97.50) than the reference group ($25.18-$76.14). As a result, the ICER associated with HIVST along with FBT was $187-$234 per additional case treated compared to FBT alone.

In a multinational study conducted in Malawi, Zambia and Zimbabwe, Mangenah et al. distributed HIVSTkits door-to-door, demonstrated to individuals the proper usage and enabled linkage to care. This was solely a costing study and outcome measures were not included. Cost per kit distributed ranged from $7.2-54.55 depending on the delivery model and location.

In an RCT conducted by Nichols et al. in Malawi individuals who sought HIV testing in an outpatient setting, the cost of diagnosis and treating new HIV cases was compared among persons who either self- tested in a facility, or who received standard or optimized provider-initiated testing and counselling. The cost of HIV testing was highest in the HIVST arm ($4.99), slightly lower in the optimized provider-initiated training and counselling group ($4.79) and was lowest in the standard of care arm ($2.44). The same trend was observed for the identification of

newly positive cases (HIVST vs. optimized vs. SOC: $189 vs. $156 vs. $101) and ART initiation ($279 vs. $156 vs. $121).

Okoboi et al. compared a novel distribution approach among men who have sex with men (MSM) of HIVST via peer networks to the traditional SOC method of performing hotspot HIVST at Uganda's The AIDS Support Organization (TASO). The study revealed that peer-distributed HIVST was more expensive than the SOC with respect to cost per case tested (peer-distributed vs. SOC: $15.90 vs. $12.40), though less expensive in regard to cost per newly identified case ($325 vs. $914) and cost per averted infection ($6,253 vs. $17,567). This suggests that when HIVST is used among high-risk populations, it can be more efficacious and therefore cost saving compared to the SOC.

Zachary and colleagues assessed the costs of introducing OraQuick, an oral HIV self-test, to the SOC in Zambia. The average unit cost of the oral self-test ranged between $3.28 and $8.17 depending on the testing algorithm.

Description of Included Modeling Studies

We identified four studies that used an economic model to examine the cost effectiveness of HIVST.

Cambiano et al[14] used a previously published HIV transmission model in 2013 to look at the impact of HIV self-testing in Zimbabwe. They made assumptions that HIVST would increase the rates of testing by 20%, halve the rates of individuals refusing to be HIV tested and substitute a portion of HIV FBT for HIVST. This was an early model and these assumptions were made through expert opinion due to a paucity ofrelevant literature. They found that implementing HIV ST would be cost-saving due to decreased testing costs. HIV ST was assumed to cost 3$ per kit compared to 10$ per kit for FBT. The study acknowledged that there was a lack of data around

infrastructure costs for self-testing but expected that HIVST would be less expensive to implement than facility-based testing due to decreased need for clinic overhead. The cost savings estimate was 75 million USD with 7000 DALYs averted over 20 years. When HIVST cost was increased, implementation was less cost effective. At a threshold of was 4$ per ST or lower, HIVST was cost effective at a willingness to pay threshold of 500 USD based on the Zimbabwean GDP.

Other factors that affected cost effectiveness were decreased rates of linkage to care and more restrictive thresholds of ART eligibility. Cambiano et al republished their updated model in 2019 to examine the implementation of HIVST in the LMIC setting[19]. They assumed an underlying test positivity rate of 3.2%but varied this parameter in sensitivity analyses. Unit testing costs for HIV ST were based off the STAR initiative reported costs of 5-11$ depending on the setting. They looked at implementation among high- risk subgroups including women having transactional sex, young people (15-24 years) and adult men (25-49 years). HIVST was cost effective among women having transactional sex with an ICER of 120 USD per DALY averted. The biggest impact in terms of cumulative DALYs averted was when HIVST was implemented among adult men, with the ICER ranging from cost saving to 260 USD per DALY averted. ST was only cost effective in Zimbabwe, when used over a five-year duration however transmission modeling was not a feature of this model.

Maheswaran et al used a Markov model to examine the cost effectiveness of HIVST in Malawi[20]. HIV test positivity rates ranged from 2-28% and were age specific. They included scenarios in which ART eligibility was restricted to CD4 counts <350uL/mL and one where everyone who was HIV positive was eligible for ART. They found that HIVST combined with facility-based testing was cost effective with an average ICER of $ 253.90 per QALY gained compared to facility-based testing alone. They included HIVrelated hospitalizations and

comorbidities in their costs.

D'Elbee analyzed the expenditure of HIVST programs across Cote D'Ivoire, Senegal and Mali[21]. They used modeling to estimate scale up costs of HIVST across different scenarios, using data from their expenditure analysis and time motion studies. They found that programmatic and personnel represented 47-78% of HIVST cost per person but decreased upon scale up due to the spreading of start-up costs across higher volumes. Average costs of HIVST upon scale up were 11-32 USD per person depending onthe subpopulation. The most expensive subpopulation to reach were people who use drugs with a cost perperson of 14-50 USD.

Discussion

HIVST is being increasingly used as a strategy to improve the uptake of HIV diagnosis, especially amongsubgroups who face barriers to accessing facility-based healthcare. We identified sixteen studies that evaluated the economics of HIVST. The majority were empiric studies that included a costing component.Three studies modeled the cost utility of HIVST[14, 19, 20], while one used a model to predict scale up costs[21].

The testing algorithm among studies, was similar with either home or facility based HIVST followed by confirmatory testing and counseling. The elements included in costing analyses varied between studies. Programmatic costs were frequently not reported, yet when included typically represented a large portionof the total cost[21]. Reported outcomes included cost per test, cost per case diagnosed, cost per case treated, ICER per case diagnosed/treated, cost per infection averted, cost per quality adjusted life year (QALY) and cost per disability adjusted life year (DALY) averted. The heterogeneity of the costs and outcomes made it impossible to conduct a meta-analysis which is why we have summarized the results innarrative format.

The heterogeneity of our results, suggest the need for standardized reporting of economic

evaluations toimprove the generalizability across studies. Studies reporting costs should aim to include overhead programmatic, costs associated with implementation and personnel costs, to avoid underestimating the total expenses associated with HIVST.

The vast majority of included studies assessed the cost effectiveness of HIVST, with only three (3/16) studies including utility measures. Utility measures, such as QALYs and DALYs, are important in economic studies because they provide information around patient important outcomes such as: quality of life rather than simply cost per case or diagnosis. Utility measures also allow for standardization across studies, which would facilitate comparison of findings.

The cost per case diagnosed ranged from $10.13-325 per case diagnosed. The range in cost estimates, likely results from the differences in the costs and implementation approaches included in the study. Forexample, the estimate of $10.13 per case represents the cost of HIVST along with a SMS based support.The Okoboi study, which estimated cost at 325 per case diagnosed, administered HIVST along with a peer-based support system among MSM to support linkage to care and ART initiation. This actually led to increased efficacy and decreased cost per case diagnosed, compared to facility-based testing. This supports the importance of HIVST programs that include resources to help connect individuals who self-test positive to confirmatory care and treatment.

Studies made conclusions around cost effectiveness using a predetermined willingness to pay (WTP) threshold. Typically, authors chose their WTP threshold based on country specific GDP per capita, although one study used 500 USD per DALY averted. All studies concluded that despite increased unit costs for HIVST compared to FBT that HIVST was cost effective among high-risk populations. There was one study that found that HIVST was not cost effective, under certain circumstances. Cambiano modeled that HIVST was only cost effective if the campaign length was under 5 years and undiagnosed HIV prevalence was over 3%. They used a relatively

conservative WTP threshold of $500 per QAL gained.

Limitations

Our study summarizes a large body of literature on HIVST, but there are several important limitations. The field of HIVST is rapidly evolving and it is likely that some of the earlier publications do not reflectthe current cost effectiveness. For example, the cost of HIVST has recently been subsidized by the Bill Gates Foundation which will change the cost effectiveness profile among many countries. The cost of HIVST diagnostics and ART vary between countries and are impacted by national negotiations and drugprocurement strategies. To mitigate this, we have limited our search strategy to the past ten years.

Economic studies are context specific and generalizing across locations should be done with caution. Many studies identified underlying prevalence of undiagnosed HIV as an important driver of cost effectiveness[14, 15, 19, 20]. This is highly dependent on the subpopulation, which is why HIVST tends to be more cost effectiveness among individuals who are at high risk for contracting HIV.

Additionally, there is likely an element of publication bias as efficacious and cost-effective interventionsare more likely to be published. This would skew our results to overestimate the cost effectiveness of HIVST.

Conclusion

HIVST is a novel approach that has been shown to improve the uptake and acceptability of HIV diagnosis. It is especially promising among high-risk subgroups that face barriers in accessing facility-based care but have a high underlying prevalence of undiagnosed HIV. This systematic review represents the first summary of the economic evidence for HIVST. Our findings suggest that HIVST can be cost effective, particularly among high-risk subgroups. We have also

identified significant heterogeneity among the costing methodology and outcomes used between studies, suggesting a need for standardization of economic research.

Table 1: Study Characteristics

Study, Year	Location	Study population	Self-screen & diagnostic tools	Reference screening strategies	Analysis Horizon	Analysis perspective
Bulterys, 2020	Uganda	Pregnant women living with HIV and their male partners	Self-test conducted at home followed by clinic-based confirmatory test, counseling and linkage to treatment/PrEP and syphilis testing	Self-test conducted at home. For males who obtain a positive self-test, linkage to clinic-based confirmatory test, counseling, linkage to treatment and extra syphilis testing	5 years	Health system
Cambiano, 2015	Zimbabwe	General public, aged 18-65 years	Self-test followed by confirmatory test	Provider delivered HIV testing and counseling	20 years	Health system
Cambiano, 2019	Sub-Saharan Africa	a) Women having transactional sex b) Young people aged 15-24 years c) Adult men, aged 25-49 years	Community based self-test followed by confirmatory test	Provider delivered HIV testing and counseling	50 years	Health system
Choko, 2019	Malawi	Male partner of antenatal clinic attendees	Self-test (+/-financial incentives, phone call reminders)	Invitation to clinic-based testing	1 year	Health system
D'Elbée, 2020	Lesotho	Residents in one of five districts of Lesotho	Two scenarios: 1- HIVST added to the existing community-based HIV testing services 2- HIVST added to the existing HIV testing services. The HIVST approach used individual	Community-based HIV testing services which offered two options: 1- Mobile outreach with tents providing testing where clients were offered a) conventional testing b) to self-test at the	2 years	Provider

Study, Year	Location	Study population	Self-screen & diagnostic tools	Reference screening strategies	Analysis Horizon	Analysis perspective
			HIVST booths wherein clients were encouraged to self-test on-site followed by on-site confirmative testing for those with reactive a self-test	tent (supervised or unsupervised) with immediate confirmatory testing available, or c) to take the kit away for use offsite 2- Index testing where counsellors travel to households and offer door-to-door testing to all in the area		
D'Elbée, 2021	Côte d'Ivoire, Senegal, Mali	Key populations (including female sex workers, men who have sex with men, and people who use drugs) in local civil society organizations	HIV self-test	Not reported	17 years	Provider
Dovel, 2020	Malawi	Adolescents and adults, aged >15 years of age	Facility-based Oraquick HIV self-test (among preliminary positives, confirmatory testing per the national testing algorithm was conducted)	Two reference groups: 1- standard provider-initiated testing and counselling, 2- optimised provider-initiated testing and counselling (with additional provider training and morning HIV testing)	4 months	Health system
George, 2018	Kenya	Truckers and female sex workers who	SMS promoting self-testing	SMS promoting clinic-based testing	1 year	Health system

Study, Year	Location	Study population	Self-screen & diagnostic tools	Reference screening strategies	Analysis Horizon	Analysis perspective
		were irregular HIV testers				
Indravudh, 2021	Malawi	Adolescents and adults, aged >15 years of age	OraQuick HIV Self-Test followed by confirmatory test	Finger-prick rapid diagnostic tests available through the Ministry of Health	4 months	Health system
Maheswaran, 2016	Malawi	General public, >18 years of age	HIV self-tests performed at home	Hospital- and clinic-based routine confirmatory HIV testing	2 years	Health system
Maheswaran, 2018	Malawi	Individuals in communities with high HIV prevalence	Facility-based HIV testing and counselling plus HIV self-testing	Facility-based HIV testing and counselling	20 years	Health system
Mangenah, 2019	Malawi, Zambia, Zimbabwe	General public, >16 years of age	HIV self-tests performed at home, with kit use demonstration. Linkage to care was supported by a community volunteer	Facility-based confirmatory testing performed for individuals who tested positive via the HIV self-test	1 year	Health system
Nichols, 2020	Malawi	Adolescents and adults, aged >15 years of age who sought HIV testing at one of 15 outpatient departments in health facilities	Facility-based HIVST (if preferred, performed at home). Among preliminary positives who disclosed their test results were linked to confirmatory testing and linkage to care	Two reference groups: 1- standard provider-initiated testing and counselling, 2- optimised provider-initiated testing and counselling (with additional provider training and morning HIV testing)	5 months	Provider
Okoboi, 2021	Uganda	Men who have sex with men, aged >18 years of age who had not tested in the past	Peer-distributed HIVST oral test kit (OraQuick Rapid HIV-1/2 Antibody Test) and peer-provided pre- and post-	Hotspot testing at the AIDS Support Organisation using blood-based	3 months	Provider

Study, Year	Location	Study population	Self-screen & diagnostic tools	Reference screening strategies	Analysis Horizon	Analysis perspective
		6 months, and who had receptive or insertional anal sex with men in the past year	test HIV counseling and follow-up through phone calls and face-to-face meetings	confirmatory HIV tests (Determine and Uni-Gold) among participants who self-tested positive		
Zachary, 2012	Zambia	General public, >18 years of age	OraQuick and determine self-tests, followed by confirmatory testing. Counselors were available to support sample collection, performance of assays, interpretation of results	None	4 months	Health system

PrEP, pre-exposure prophylaxis; HIVST, human immunodeficiency virus self-testing; SMS, short message service

Table 2: Results

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
Bulterys, 2020	Modeling	Self-test conducted at home followed by clinic-based confirmatory test, counseling and linkage to treatment/PrEP and syphilis testing	HIVST cost: $3.05	Cost per female case self-tested	Counseling provided individually: A) Using research staff salaries: $13.96 B) Using government health sector salaries: $9.45 Counseling provided in group sessions: $3.70
				Cost per male case tested at a clinic	All males performed confirmatory testing: A) Using research staff salaries: $20.02 for HIV-positive and $18.68 for HIV-negative males B) Using government health sector salaries: $16.00 for HIV-positive and $15.12 for HIV-negative males
Cambiano, 2015	Modeling	Self-test followed by confirmatory test	HIVST cost: Average $3	Costs and DALYs averted	Implementation of HIVST was cost saving ICER compared to FBT was $10,714 saved per DALY averted
Cambiano, 2019	Modeling	Community based self-test followed by confirmatory test	HIVST cost: $10.18 for Zimbabwe and $5.82 for	Cost per DALY averted	Zimbabwe- WTS 120 per DALY Malawi- WTS 60 per DALY Zimbabwe- Young people 2000 per DALY

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
			Malawi		Malawi- Young people 1100 per DALY Zimbabwe- Adult men 880 per DALY Malawi- Adult men 520 per DALY
Choko, 2019	Empiric	Oraquick HIVST followed by clinic testing if positive with varying financial incentives	Intervention cost: $3,446.03 (for 442 participants)	Cost per case diagnosed	$23.73-$28.08 per case (depending on financial incentive) ICER= 222 per additional person started on ART
D'Elbée, 2020	Empiric	HIVST offered (added to community-based HIV testing services). In a separate scenario where HIVST booths were used, clients were encouraged to follow their self-test with an immediate on-site confirmatory test for those with a reactive self-test	HIVST cost: US$2.71	Cost per case tested via community-based HIV testing	When only community-based testing was offered: $32.2 When HIVST was offered: $25.0 When HIVST using individual booths was offered: $34.3
				Cost per case tested via HIVST	When HIVST was offered: $15.4 When HIVST using individual booths was offered: $14.0
				Cost per case diagnosed	When only conventional community-based testing was offered: US$956 When HIVST was offered: US$1,249

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
					When HIVST using individual booths was offered: US$813
D'Elbée, 2021	Empiric	Not reported	Côte d'Ivoire: $2.68 Senegal/Mali: $3.08	Cost per case tested	Côte d'Ivoire: $13 per WTS, $15 per men who have sex with men and $16 per a person who uses drugs Senegal: $17 per WTS, $27 per MSM, $144 per PWUD Mali: $16 per WTS, $28 per MSM
				Average scale-up cost	Côte d'Ivoire: $9 per WTS, $9 per MSM, $14 per PWUD Senegal: $13 per WTS, $23 for MSM, $50 per PWUD Mali: $10 per WTS, $17 per MSM
Dovel, 2020	Empiric	Oraquick HIVST administered to all in the HIVST group. Among those with HIVST-positive results, confirmatory testing per the national testing algorithm was conducted: Determine 1/2 and Uni-Gold	Average $4.99 per ST	Cost per case tested	Standard provider-initiated testing and counselling group: $2.44
				Cost per newly identified positive case	HIVST group: $189 Standard provider-initiated testing and counselling group: $101 Optimised provider-initiated training and counselling group: $156

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
				Cost per ART initiation	HIVST group: $279 Standard provider-initiated testing and counselling group: $121 Optimised provider-initiated training and counselling group: $156
George, 2018	Empiric	SMS system promoting community based HIVST (taken either at home or in clinic)	Bottom up microcosting approach $10.13 per ST	Cost per case tested	0.15 per additional client tested
Indravudh, 2021	Empiric	Community based OraQuick HIV self-test followed by confirmatory test	$5.70 per ST	Cost per case diagnosed	Cost per HIV-positive identified: $241 Cost per new HIV-positive identified: $602 Cost per HIV-positive identified not on treatment: $468
Maheswaran, 2016	Empiric	Not reported	Average HIVST cost: $8.78	Cost per case diagnosed	Self-test: $97.50 Facility-based: $25.18-$76.14
				Health provider facility-based testing cost	$7.53-$10.57
				ICER	$187-234 per case treated

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
Maheswaran, 2018	Modeling	Not reported	HIVST cost: $8.78	Health provider facility-based testing cost	$8.90
				ICER	$253.9 per QALY
Mangenah, 2019	Empiric	HIV self-test followed by confirmatory testing for individuals with reactive self-test results	Average HIVST kit cost: $8.15 in Malawi, $16.42 in Zambia, $13.84 in Zimbabwe	NA	NA
Nichols, 2020	Empiric	HIVST administered to all in the HIVST group. Among those who disclosed HIVST-positive results, confirmatory testing was arranged	HIVST cost: $0.80-$1.00	Cost per case tested	HIVST group: $4.99 Standard provider-initiated testing and counselling group: $2.44 Optimised provider-initiated training and counselling group: $4.79
				Cost per newly identified case	HIVST group: Average $189; $204 for adult women, $237 for adolescents, $124 for men Standard provider-initiated testing and counselling group: Average $101 Optimised provider-initiated training and counselling group: Average $156

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
				Cost per ART initiation	HIVST group: $289 Standard provider-initiated testing and counselling group: $121 Optimised provider-initiated training and counselling group: $156
Okoboi, 2021	Empiric	OraQuick HIVST oral test performed followed by confirmatory testing for individuals with reactive self-test results	HIVST cost: $6.72	Cost per case tested	HIVST group: $15.90 Standard hotspot HIV testing group: $12.40
				Cost per newly identified case	HIVST group: $325 Standard hotspot HIV testing group: $914
				Cost per averted infection	HIVST group: $6,253 Standard hotspot HIV testing group: $17,567
				ICER	Per test: $112.3 Per averted infection: $1727
Zachary, 2012	Empiric	Determine and OraQuick tests performed; if one or both are positive, Uni-Gold test conducted, and if positive, participant considered to be HIV positive. In the case of	Average unit cost (varying two-test algorithms and HIV prevalence	NA	NA

Study, Year	Type of Study	Self-Testing Algorithm	Cost (Unit)	Outcome Assessed	Outcome Result (USD, 2019)
		invalid initial results, tests were repeated. If Determine and OraQuick tests yielded negative result, participant is considered to be HIV negative	rates): $3.28-$8.17		

PrEP, pre-exposure prophylaxis; HIVST, human immunodeficiency virus self-testing; SMS, short message service; DALY, disability adjusted life year; ICER, incremental cost effectiveness ratio; FBT, facility-based testing; WTS, women having transactional sex; MSM, men who have sex with men; PWUD, people who use drugs;

References

1. Stevens DR, Vrana CJ, Dlin RE, Korte JE. A Global Review of HIV Self-testing: Themes and Implications. AIDS Behav. 2018;22: 497-512.
2. Eshun-Wilson I, Jamil MS, Witzel TC, et al. A Systematic Review and Network Meta-analyses to Assess the Effectiveness of Human Immunodeficiency Virus (HIV) Self-testing Distribution Strategies. Clin Infect Dis. 2021;73: e1018-e1028.
3. MacGowan RJ, Chavez PR, Borkowf CB, et al. Effect of Internet-Distributed HIV Self-tests on HIV Diagnosis and Behavioral Outcomes in Men Who Have Sex With Men: A Randomized Clinical Trial. JAMA Intern Med. 2020;180: 117-125.
4. Jamil MS, Prestage G, Fairley CK, et al. Effect of availability of HIV self-testing on HIV testing frequency in gay and bisexual men at high risk of infection (FORTH): a waiting-list randomised controlled trial. Lancet HIV. 2017;4: e241-e250.
5. Katz DA, Golden MR, Hughes JP, Farquhar C, Stekler JD. HIV Self-Testing Increases HIV Testing Frequency in High-Risk Men Who Have Sex With Men: A Randomized Controlled Trial. J Acquir Immune Defic Syndr. 2018;78: 505-512.
6. Krause J, Subklew-Sehume F, Kenyon C, Colebunders R. Acceptability of HIV self-testing: a systematic literature review. BMC Public Health. 2013;13: 735.
7. Harichund C, Moshabela M. Acceptability of HIV Self-Testing in Sub-Saharan Africa: Scoping Study. AIDS Behav. 2018;22: 560-568.
8. Kelvin EA, George G, Mwai E, et al. A Randomized Controlled Trial to Increase HIV Testing Demand Among Female Sex Workers in Kenya Through Announcing the Availability of HIV Self-testing Via Text Message. AIDS Behav. 2019;23: 116-125.
9. Kelvin EA, George G, Mwai E, et al. Offering self-administered oral HIV testing to truck drivers in Kenya to increase testing: a randomized controlled trial. AIDS Care. 2018;30: 47-55.
10. Pai N, Esmail A, Saha Chaudhuri P, et al. Impact of a personalised, digital, HIV self-testing app-based program on linkages and new infections in the township populations of South Africa. BMJ Glob Health. 2021;6.
11. UNAIDS. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic. Retrieved September 8, 2021 from https://www.unaids.org/en/resources/documents/2017/90-90-902017.
12. HIVST.org. HIV self testing research and policy hub. Retrieved September 8, 2021 from http://www.hivst.org/2019.
13. Rivera AS, Hernandez R, Mag-Usara R, et al. Implementation outcomes of HIV self-testing in low- and middle- income countries: A scoping review. PLoS One. 2021;16: e0250434.
14. Cambiano V, Ford D, Mabugu T, et al. Assessment of the Potential Impact and Cost-effectiveness of Self-Testing for HIV in Low-Income Countries. J Infect Dis. 2015;212: 570-577.
15. Choko AT, Corbett EL, Stallard N, et al. HIV self-testing alone or with additional interventions, including financial incentives, and linkage to care or prevention among male partners of antenatal care clinic attendees in Malawi: An adaptive multi-arm, multi-stage cluster randomised trial. PLoS Med. 2019;16: e1002719.
16. The World Bank (2021). The World by Income and Region. Retrieved May 1, 2021 from https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.
17. Arya S, Kaji AH, Boermeester MA. PRISMA Reporting Guidelines for Meta-analyses and Systematic Reviews. JAMA Surg. 2021;156: 789-790.

18. World Bank. Inflation, consumer prices %, 2020.
19. Cambiano V, Johnson CC, Hatzold K, et al. The impact and cost-effectiveness of community-based HIV self-testing in sub-Saharan Africa: a health economic and modelling analysis. J Int AIDS Soc. 2019;22 Suppl 1: e25243.
20. Maheswaran H, Clarke A, MacPherson P, et al. Cost-Effectiveness of Community-based Human Immunodeficiency Virus Self-Testing in Blantyre, Malawi. Clin Infect Dis. 2018;66: 1211-1221.
21. d'Elbee M, Traore MM, Badiane K, et al. Costs and Scale-Up Costs of Integrating HIV Self-Testing Into Civil Society Organisation-Led Programmes for Key Populations in Cote d'Ivoire, Senegal, and Mali. Front Public Health. 2021;9: 653612.

Chapter Three

Our review of the economic literature suggested that HIVST could be cost effective, depending on the context. This project was commissioned by FIND, with the objective to create a model that could estimate cost utility across different contexts.

The next step of this project was to model the cost utility of HIVST through an economic model. We used the epidemiological and cost inputs from our literature review to build a model that evaluates the cost utility of HIVST using a combined decision tree and Markov model. With this model, we were able to identify the key drivers of cost effectiveness for HIVST through deterministic analysis. The model is modifiable with key model inputs that can be overridden to reflect context specific factors; for example, HIV prevalence and ST kit cost can be input with regional data to provide a more accurate cost effectiveness estimate.

HIVST can be conducted in a variety of settings, including through the home or in a facility[45]. When HIVST is administered at home, there is increased risk of loss to follow up[46]. This is likely because individuals must take an extra step to link to clinic-based confirmatory testing and ART initiation. There has been increasing interest in administering HIVST with adjunctive programs that support linkage to care. This can involve a variety of different strategies, including using community-based methods that use resources within the community to follow up on self-tests. An example of a community-based program would be using community volunteers to go house to house to follow up on self-testing and provide education around next steps[47-49]. As the internet becomes more globally accessible, digital based approaches have been gaining attention[50]. Digital based approaches may also be more appealing to the public, as they preserve anonymity. An example of a digital- based approach would be advertising HIVSTand providing post-test counselling through a website or using text messages to follow up on self-testing results[51, 52].

Our model uses cost and effectiveness data from published community-based and digital-based interventions to understand how these programs impact the cost utility of HIVST. Our model was unique, as it is the first published economic model to assess the economic impact of community and digital based programs that support linkage to care with HIVST. These programs are associated with an additional cost,but if they improve linkage to care and the overall effectiveness of HIVST they could ultimately be cost effective. Given the constraints of a resource-limited health care system, it is important to understand how different approaches to HIVST impact overall cost utility in order to optimize resource utilization.

An Economic Model for HIV Self-Testing

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Background

The United Nations General Assembly has set ambitious targets for HIV diagnosis and care to be met by the end of 2030[1]. Although global gains have been made, many countries have yet to meet critical targets[2-4]. There have been significant advances in diagnostic technologies and novel treatment and supportive care options for HIV however health care advances may not benefit LMICs, given challenges with underlying health care system infrastructure[5].

An innovative method to promote HIV screening and diagnosis is HIV self-testing (HIVST), where individuals can perform their own HIV screen. HIVST provides an anonymous method for testing that may be more convenient and approachable than accessing testing through conventional health clinics. When paired with education and supports ensuring linkage to confirmatory testing, treatment and follow-up care, self-testing is a promising strategy mitigating the global HIV burden.

HIVST is done on oral fluid or blood and requires the user to interpret the result and seek follow-up care as needed. The test can be supervised (with a health care worker or volunteer watching) or unsupervised (within a clinic or at home). The test result is available within minutes with positive self-tests requiring confirmatory diagnostics. Previous literature strongly suggests HIVST is preferred by clients with increased rates of uptake compared to conventional testing[6-8]. A recent scoping review found the major factors contributing to increased acceptability of HIVST (compared to facility-based testing) were convenience, stigma reduction and self-control.

Population level screening programs including those utilizing HIVST can be resource-intense and economic evidence is critical in providing evidence to guide implementation and scale-up of such programs. Past studies have suggested that HIVST can be cost effective, depending on the context and specific intervention used[9-15]. This has been shown among the general population, but also among marginalized and conventionally hard-to-reach groups such as sex workers, truck drivers and homeless populations[16-18].

While there are many advantages of HIVST, concern has been raised around linkage to care with some studies suggesting that linkage to care could be lower with HIVST (particularly with home-based approaches)[19-21]. A variety of different approaches have been used with HIVST to support and improve uptake and linkage to care, including community-based and digital-based programs. HIVST with community-based support involves using resources from within the community, such as existing health infrastructure, volunteers or peer support groups to help offer HIVST kits, support uptake and linkage to care[13].

HIVST with digital-based support includes the use of digital interventions such as SMS messaging, websites, downloadable applications and social media to improve the uptake, help with user experience and ease of testing, provide online counselling or call-in support for linkage to counselling, clinical care and follow-up. As access to the internet improves at a globally[22], HIVST with digital support offers improved accessibility and confidentiality for HIVST especially among hard-to-reach populations[23] or stigmatized groups, and evidence supporting the efficacy of digitally supported HIVST is growing[24].

The aim of this work is to assess the cost effectiveness of various testing strategies for HIVST employing either community-based or digital based supports using a combined Markov and decision tree model using the health care system perspective. We have modeled the cost utility of HIVST with either community-based or digital-based supports in addition to facility-based testing (FBT) compared to FBT alone across emblematic scenarios representative of Malawi, South Africa and Brazil. An additional emblematic scenario, set in Thailand, is included in the appendices.

To our knowledge, this is the first model seeking to understand the cost-effectiveness of employing either digital or community-based interventions along with HIVST.

Methodology

Design:

Our hypothesis was that HIVST (along with FBT) would be associated with increased diagnosis of HIV

within the modeled population and decrease the burden of HIV-related morbidity and mortality compared to FBT alone. We wanted to understand what the cost per utility (DALY averted) of adding HIVST to FBT would be within a LMIC.

We used an embedded decision tree within a Markov structure to assess the cost-utility of HIVST using TreeAge Pro 2021, R1 (decision tree software)[25]. We used a decision tree to capture ST and diagnostic testing process and a Markov model for the chronic health states of HIV positive (treated and untreated), HIV negative and death. Cycle length was one year, and time horizon was 30 years.

Patient Population:

We modeled the cost effectiveness of HIVST within the general population (ages 15-65) with unknown HIV status. We did not include individuals who were already known to be HIV positive. We included sub-analyses where HIVST was restricted to high-risk subpopulation, men who have sex with men (MSM).

Comparator:

HIVST along with FBT was compared to the current standard of care, which was facility-based testing alone.

Setting:

The model was set in a base case scenario, within a LMIC context. The emblematic scenarios were modeled in Malawi, South Africa and Brazil and were selected to represent low income/high HIV prevalence, middle income/high HIV prevalence and middle income/low HIV prevalence populations. The emblematic scenario of Thailand was requested by FIND.

Data Collection:

The results of a previously conducted literature review have been used to inform the inputs (epidemiological, cost and outcome) of the economic model. For the base case scenario, costs were extracted from the studies included in the systematic review and were averaged (table 2). For the emblematic scenarios, we used data from specific interventional studies to parametrize each emblematic

scenario model. The specific HIVST modeled was OraQuick™, which was the ST most commonly used in the existing economic literature within LMICs[26-30]. Sensitivity and specificity of the HIVST was varied in deterministic analysis.

Epidemiological Parameters

For the probability of developing a new HIV infection, the average probability of developing a new infection across all LMIC countries was used, sourced from the UNAIDS database[4]. In each emblematic scenario, country-specific data was used. For underlying HIV test positivity probabilities, an average was calculated from our literature review which looked at the current economic data for HIVST. HIV test positivity rate was modeled at 5% for the base case and varied between 1-15%. For emblematic scenarios, HIV test positivity rates were based on published literature or UNAIDS reported HIV incidence rates. Linkage to care was defined as follow up to confirmatory facility diagnostic testing after HIVST. PrEP has been included in our model as it is increasingly used in high-risk subpopulations [31]. Those who were on PREP had a lower risk of contracting HIV and a higher rate of linking to care and accepting ART.

Cost Effectiveness Approach

HIVST was costed in our base case scenario using the average cost per HIVST (including unit test costs and implementation costs) extracted from our literature review. Costs per HIVST kit in the base case scenario was $7 per person and FBT was $5 per person[16, 21, 22, 39-43]. The emblematic scenarios analyzed the cost of HIVST coupled with either a community or digital based intervention that helped to support linkage to care and follow. For the emblematic scenario estimates, the model was parametrized with HIVST programmatic costs from the corresponding study.

Primary outcome was the incremental cost effectiveness ratio (ICER) measured as the incremental cost in USD per disability-adjusted life year (DALY) averted[32]. All ICER calculations were performed with FBT alone as the reference case.

ICER estimates were compared against a willingness to pay threshold established a priori to determine

whether the intervention should be considered cost-effective. As per the WHO Choosing Interventions that are Cost-Effective (CHOICE) guidelines[33], the intervention will be considered cost-effective if it is under three times the local GDP per capita per DALY averted and highly cost-effective if it is under the GDP per capita. GDP per capita was sourced from the World Bank Data base.[34]

In terms of costs, we have taken a health care system perspective as there was very little data to inform patient incurred costs. In addition, HIV testing and treatment is most commonly incurred by the health system and not individual insurance. All of the countries modeled in the emblematic scenarios have publicly funded HIV testing and treatment available. A mid cycle correction was applied to costs and utilities. Both costs and utilities are discounted at 3% per annum. All costs were converted [35], adjusted for inflation[36, 37] and converted into 2020 USD.

Sensitivity Analyses

Uncertainty was explored through one and two-way sensitivity analyses to understand the impact of key parameters on model results and to identify key drivers of cost-effectiveness. Key parameters identified a priori include test positivity, programmatic costs of HIVST, HIVST kit costs, HIVST uptake, linkage to care and ART initiation rates[10, 11, 38, 39].

A probabilistic sensitivity analysis was undertaken using 10,000 Monte Carlo repetitions. Costs are represented by gamma distributions, transitional probabilities are modeled by beta distributions and utility values modeled using triangular distributions.

The unit costs employed in the model go beyond just HIVST kit costs and include programmatic costs associated with program implementation. However further benefits associated with economies of scale were not included. For example, the cost of setting up infrastructure to support HIVST is included as an average per person tested. Because of this, increased uptake of HIVST always incurs more costs. To address this, a sensitivity analysis was performed where the programmatic portion of HIVST is divided by an increasing number of people to assess how increased uptake leading to reduced unit test costs might

affect model estimates.

Results:

For our base case scenario, using average HIVST costs, HIVST in addition to FBT was associated with an ICER of $512.74 /DALY averted compared to FBT alone (table 3). Probabilistic analysis showed that there is an 85% chance that HIVST would be cost-effective at a using a WTP threshold of $810 and this was considered highly cost effective.

The tornado diagram (figure 3) illustrates the influence of HIVST cost where HIVST was only cost effective at the given threshold if the cost per test remained under $10.7. Increasing ART costs can also be influential with worsening cost-effectiveness estimates due to increasing costs associated with long-term ART. Linkage to care is an important determinant, with increasing linkage to care improving cost-effectiveness, and a minimum linkage of 25% needed to meet the WTP threshold. Increasing HIV test positivity also improves cost-effectiveness, with a 1% minimum for cost-effectiveness.

Malawi

Community based intervention:

The CB model for Malawi is based on data from a study conducted by Indravudh et al[13] where volunteers worked with health officials to identify barriers to HIVST within their community and created solutions to overcome them. HIVST kits were broadly distributed throughout rural villages for community members to use at their own convenience, with follow-up care, testing, counselling and treatment available at existing health care facilities, the rate of test return was 75%. The campaign included support for linkage to care, that was individualized to each community. The cost reported per ST returned was $5.7 USD, this includes test kit costs and consumables, implementation costs and stipends paid to community volunteers. Our model made the assumption that ART eligibility was limited to those with a CD4+ count <500cells/uL. Given the low accessibility and uptake of PREP in LICs such as Malawi, we assumed no access to PrEP into this scenario.

Using HIVST costs, uptake and follow up data from the referenced study[13], along with region specific HIV test positive and infection rates, ART costs and population mortality rates we estimated an ICER of $485.71/DALY averted (table 3) for HIVST with CB support compared to FBT alone, finding HIVST in addition to FBT would be cost-effective compared to FBT alone in only 7% of the probabilistic scenarios based on Malawi's GDP per capita of $411 USD (figure 4). If using a more liberal WTP threshold of 3xGDP per capita, HIVST in addition to FBT would be considered cost-effective in 98% of the probabilistic scenarios run compared to FBT alone (figure 5).

The drivers of the ICER for HIVST in Malawi using a community-based intervention were cost of the ST kit, ART cost and HIV test positive rates within the population. Deterministic analysis varied all inputs within a reasonable range, but there was no threshold at which any of the key drivers resulted in HIVST being cost effective at a WTP threshold of the Malawian GDP per capita (figure 6).

Digital Based Intervention:

For our Malawi digital based (DB) model, parameters relevant to the DB intervention such as cost, uptake and linkage to care were sourced from a large study conducted in Kenya, using SMS based messaging to target truck drivers and female sex workers (FSWs) for HIVST[12, 40]. The HIVST along with the digitally based intervention costed $11.45 per ST, SMS costs were $0.03 per text[40]. We assumed in this scenario, that the entire eligible population received an SMS message and only those who participated in HIVST (10.1%) incurred ST kit costs.

We found that HIVST with FBT along with a DB intervention was associated with an ICER of $673.70/DALY averted (table 3), with HIV ST cost effective compared to FBT alone in only 0.2% of cases (figure 7). Using a WTP threshold of 3x the Malawian GDP per capita, the probability that HIVST would be cost effective compared to FBT alone increased to 94% (figure 8).

<u>Brazil</u>

Community Based:

The CB model for Brazil is based on data from a study conducted by DeCruz et al[41] where a mobile testing unit (MTU) distributed kits among an MSM population. This study found that rates of linkage to care varied from 23% for the MTU, to 74% at the government run health facilities. This study did not include rates of ART initiation and our model was supplemented by other studies for this input[42, 43]. This scenario assumed all new HIV diagnoses were eligible to initiate ART and PREP was modeled for high-risk populations.

Using a WTP threshold corresponding to Brazil's GDP per capita ($8,717), HIVST with a CB intervention would was not highly cost effective with an average ICER per DALY averted of $20,032.83 USD (table 3). Using a WTP of 3 x GDP per capita (26,151.6), HIVST with a DB intervention was cost effective in 71% of the probabilistic scenarios (figure 9).

The probabilistic analysis showed that the probability that HIVST would be cost effective at a WTP threshold of $8717 was 1.7% (figure 10). The key determinants of cost effectiveness within this scenario were linkage to care, cost of the ST kit and HIV test positivity rates. At a WTP threshold of $8717 USD HIVST was cost effective when linkage to care was over 83%, when the cost of HIVST per person was under $18 USD and when the HIV test positive rate was >4% (figure 11).

Digital Based:

The DB intervention from Brazil is based on a study conducted by De Boni et al[15], using a website targeting an MSM population to facilitate HIVST. Return of STs that was 21.4%, with 7% of those who visited the website ordering tests. Inputs for linkage to care and ART initiation were supplemented from other studies[31, 41, 42].

Using a WTP threshold of GDP per capita ($8717), HIVST with a DB intervention would be cost-effective with an ICER of $2028/DALY averted (table 3). Probabilistic analysis indicated that HIVST using DB would have over a 99% probability of being cost effective at a WTP threshold of $8717 in the Brazilian setting (figure 12).

To examine the impact of targeting the intervention to high risk subgroups, with increased HIV prevalence, we modeled the cost-effectiveness of a DB intervention limited to the MSM population, using test positivity of 7.5% based on reported HIV incidence data among MSM from Brazil[44, 45].

We found that HIVST with a DB support was slightly more cost-effective within this subgroup, with an ICER of $1,756/DALY averted, compared to $1,949 USD per DALY averted when implemented among the general population (table 3). Increasing uptake of PREP among this population, decreased the cost effectiveness of HIVST by decreasing HIV infection rates and underlying seropositivity of the group. There were factors that impacted the ICER value for HIVST among the MSM subgroup including yearly ART costs, HIVST cost per person, acceptability of ART and PREP use. HIVST remained highly cost effective in MSM despite varying these factors through deterministic analysis (figure 13).

South Africa

Community based:

The model for CB HIVST in South Africa was based on a study by Pettifor et al, which looked at implementing HIVST among young women in rural regions of South Africa[7]. HIVST were universally distributed to women with 92% returning tests, and 58% of positive tests linking to care. This study did not contain costing data, so costing for a similar intervention were extrapolated from a study done in Lesotho[10], with increased uncertainty ranges for probabilistic analysis.

Our model predicted that the CB intervention would be cost effective using a WTP threshold of the South African GDP per capita of $6001 with an ICER of $1753 USD/ DALY averted (table 3). Probabilistic analysis showed that chance that HIVST would be cost effective when implemented through a community-based approach was 99.4% (figure 14).

Digital Based:

There were no published studies identified through our literature review that assessed costs for DB interventions for HIVST in South Africa. We therefore extrapolated data from the Brazilian study on DB

HIVST (as previously described)[15] and applied a corrective ratio. Using this ratio, we used a cost per HIVST with a digital based intervention of $99.58 USD per test. Our model predicts that DB HIVST intervention would be highly cost effective when implemented within South Africa with an ICER of $4596.06/DALY averted (table 3) below the WTP threshold of $6001.

Drivers of cost effectiveness within this model were HIV test positive rates (where the intervention was cost effective with a test positive rate >6.5%), acceptability of ART (where the intervention was cost effective with over 50% ART initiation) and cost of the intervention (where the intervention was cost effective under 133.62 USD per person) as illustrated in figure 15.

Sensitivity Analysis: HIVST Uptake

To assess the potential impact of economies of scale on unit cost per person and cost-effectiveness we performed a sensitivity analysis in which a proportion of the HIVST cost, representing the implementation or "one time programmatic" costs were divided among an increasing number of participants. This analysis showed that as uptake increases, the cost per person decreases and HIVST becomes increasingly cost effective (figure 16).

Discussion

Our model suggests that HIV ST + FBT was more effective than FBT alone but was associated with an additional cost per DALY averted. In all scenarios assessed, HIVST in addition to FBT was considered cost effective at a WTP threshold of 3 -fold the GDP per capita. Cost effectiveness of HIVST varied between scenarios with an average ICER per DALY averted ranging from $485-20,0033 USD depending on the context and ST program used.

As internet access becomes increasingly available across countries, DB approaches offer a promising avenue to promote HIVST while maintain anonymity. They can be paired with websites and applications that focus on high-risk subgroups, for example MSM dating applications[15]. A recent systematic review found that DB applications were associated with a 1.5 times increased rate of HIVST among the MSM

population and were perceived as more accessible and convenient[46]. Interest in the use of digital platforms to promote HIVST is increasing, and this is the first model to our knowledge that evaluates the cost utility of digital based interventions. Our model supports that HIVST, delivered with a digital based intervention can be cost effective depending on the targeted population and WTP threshold.

The WTP threshold chosen was the GDP per capita of the country, which has implications for health equity. An intervention that was cost effective in South Africa, has a much lower chance of being cost effective in Malawi depsite similar efficacy, due to Malawi's lower GDP per capita. Despite this, the potential for DALYs averted is actually higher when HIVST is used in Malawi, due to the higher underlying HIV test positivity rates. Despite the increased potential to improve outcomes in LICs with higher endemic HIV rates, the methodology of comparing cost utility to GDP per capita makes HIVST much less likely to be considered cost effective. The method of determining WTP is not universally agreed upon and several alternative solutions have been proposed including using opportunity costs, where a proposed intervention is compared to an already established intervention[47, 48]

The major drivers of cost effectiveness in our model were consistent across different emblematic scenarios, including HIV prevalence, linkage to care, acceptability of ART and cost of the HIVST. A recent systematic review, suggested that HIVST may be associated with lower linkage to care compared to FBT[49]. Our inclusion of varied community based, and digital based intervention models show how different programs have highly variable rates of linkage to care. This highlights the emerging opportunity to use digital based support in conjunction with HIVST to help testing become more accessible to communities, especially among those who face barriers to accessing health care through traditional means. From a health policy perspective, it is imperative that these key drivers of cost effectiveness are considered in the planning of HIVST programs. In countries with low endemic rates of HIV, HIVST should be targeted to high-risk populations. HIVST should ideally be enacted with support for linkage to confirmatory testing and ART initiation to ensure that the program is effective.

Our results also highlight how cost effectiveness estimates vary significant across different contexts. Similar interventions, implemented in different contexts had significantly different rates of linkage to care and ART initiation which were key drivers in the cost utility estimate. There was a lack of data on the impact of HIVST on long term ART initiation and adherence. We could not identify any literature that included ART adherence after three months post HIVST. There was also a paucity of economic data regarding HIVST within Asia. We extrapolated studies from Vietnam to Thailand but did not identify any studies including costing data on HIVST from Asia. These are gaps in the literature that would be important to address in future studies.

Limitations

Although we did account for new HIV infections over time, our model did not include dynamic transmission or account for the potential impact of HIVST on transmission and the underlying community prevalence of HIV. Earlier HIV diagnosis has the potential to increase pre-symptomatic treatment and decrease transmissibility. Without including dynamic transmission modeling, the cost effectiveness of HIVST will be underestimated.

Additionally, there were gaps in the literature that required us to extrapolate between locations. We used data from a Brazilian study[15] to model a digital based HIVST approach in South Africa, because we were unable to find any appropriate studies from South Africa. Given the variability in HIVST uptake, linkage to care and ART initiation between different interventions, the results from extrapolated data should be interpreted carefully. To ameliorate this, we have varied all inputs in our deterministic analysis to show the impact on the cost utility estimate.

Key Policy Implications

Self-testing is a diagnostic strategy that can improve uptake of HIVST, particularly among hard-to-reach populations. Based on our model, ST can be cost effective depending on your underlying HIV test rate, linkage to care and HIVST costs. Among populations with low endemic rates of HIV, HIVST is most

likely to be cost effective when implemented among high-risk subgroups. Strategies to improve cost utility include decreasing programmatic and testing material costs, improving uptake of ST and supporting linkage to care. Linkage to care and initiation of ART is highly variable depending on the programmatic components of HIVST. HIVST that is provided with digital based supports, can improve cost effectiveness (despite increasing overall costs) by increasing linkage to care.

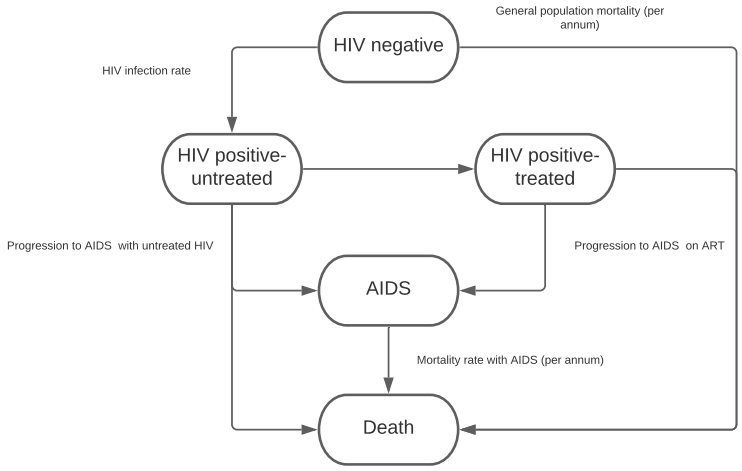
Conclusions around cost effectiveness are based on WTP thresholds, which our model calculated by GDP per capita. This led to HIVST being less likely to be cost effective in lower income countries despite leading to larger relative reductions in HIV-related morbidity and mortality. Cost utility estimates should be interpreted in the context of competing interventions within the health care system, to optimize overall population health.

Conclusion:

Self-testing is a promising new strategy that may improve access to diagnosis of infectious disease among hard-to-reach populations. Both digital based and community-based interventions have the ability to promote HIVST and improve linkage to care and rates of ART initiation (which are key drivers of cost effectiveness).

Figures:

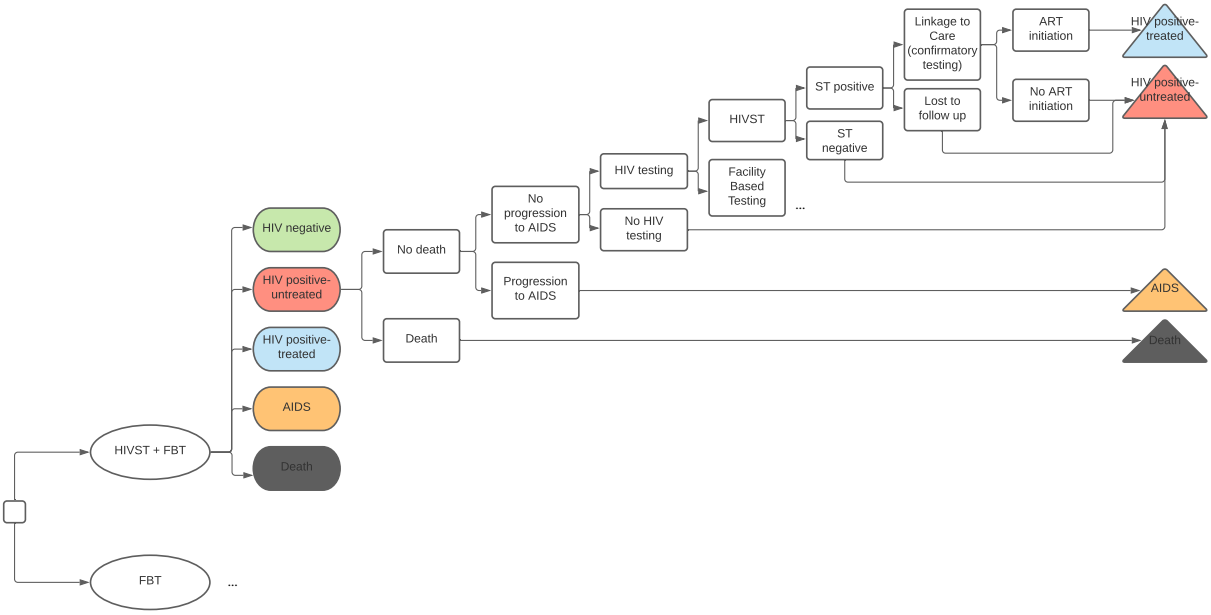
Figure One: Markov Model Schematic



AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; ART, antiretroviral therapy

This figure shows the general schema of the Markov model and how the cohort moves between different Markov states. The transitional probabilities between states are also labeled on the diagram. Individuals enter the model through either the HIV positive (undiagnosed) or HIV negative state. With each Markov cycle, there is a transitional probability to undergo HIV testing. For individuals who are diagnosed, they can either be treated or choose not to start ART. With each cycle there is transitional probability for new HIV infection or death. The probability of death is dependent on the Markov state, with those within the AIDS Markov state having a higher probability of death.

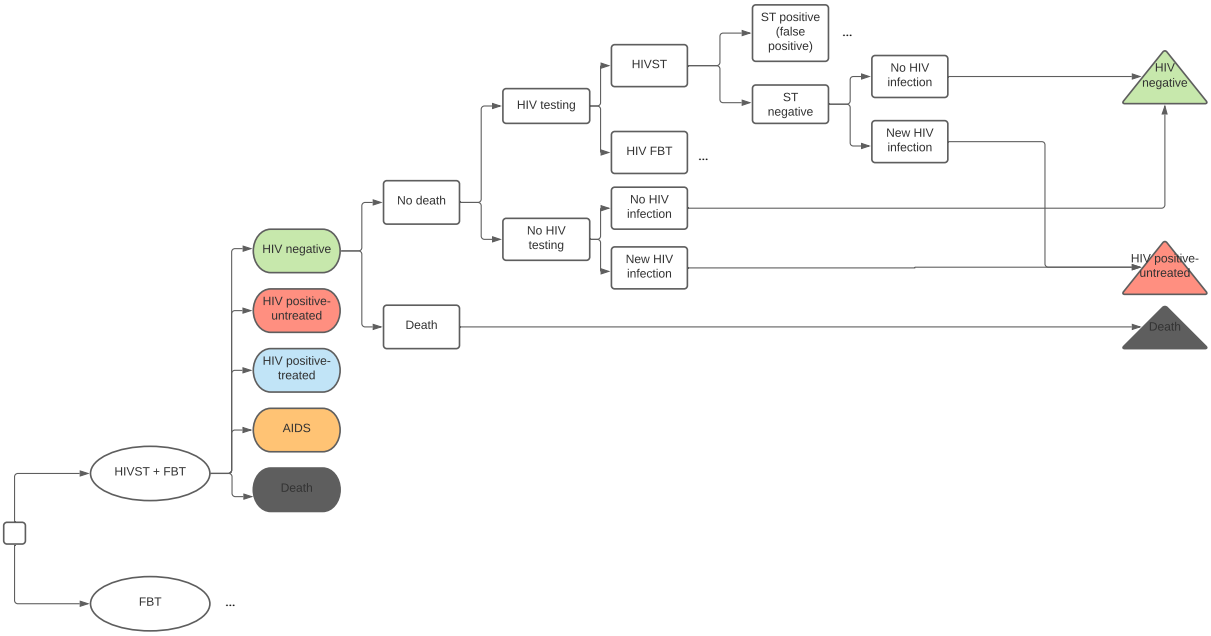
Figure Two (a): Decision Tree for HIV positive Markov state



HIVST, HIV self-testing; FBT, facility-based testing; AIDS, acquired immunodeficiency syndrome; ST, self-testing; ART, antiretroviral therapy

This diagram illustrates the combined decision tree and Markov structure of the economic model. We have compared HIVST in addition to the FBT (the standard of care) to FBT alone. The color coded ovals in this diagram represent Markov states. The cohort progresses through the decision tree structure with every Markov cycle and a proportion of the cohort may progress to a different Markov state as illustrated by the terminal triangles. This diagram shows how PLHIV who are untreated may transitioned to starting ART.

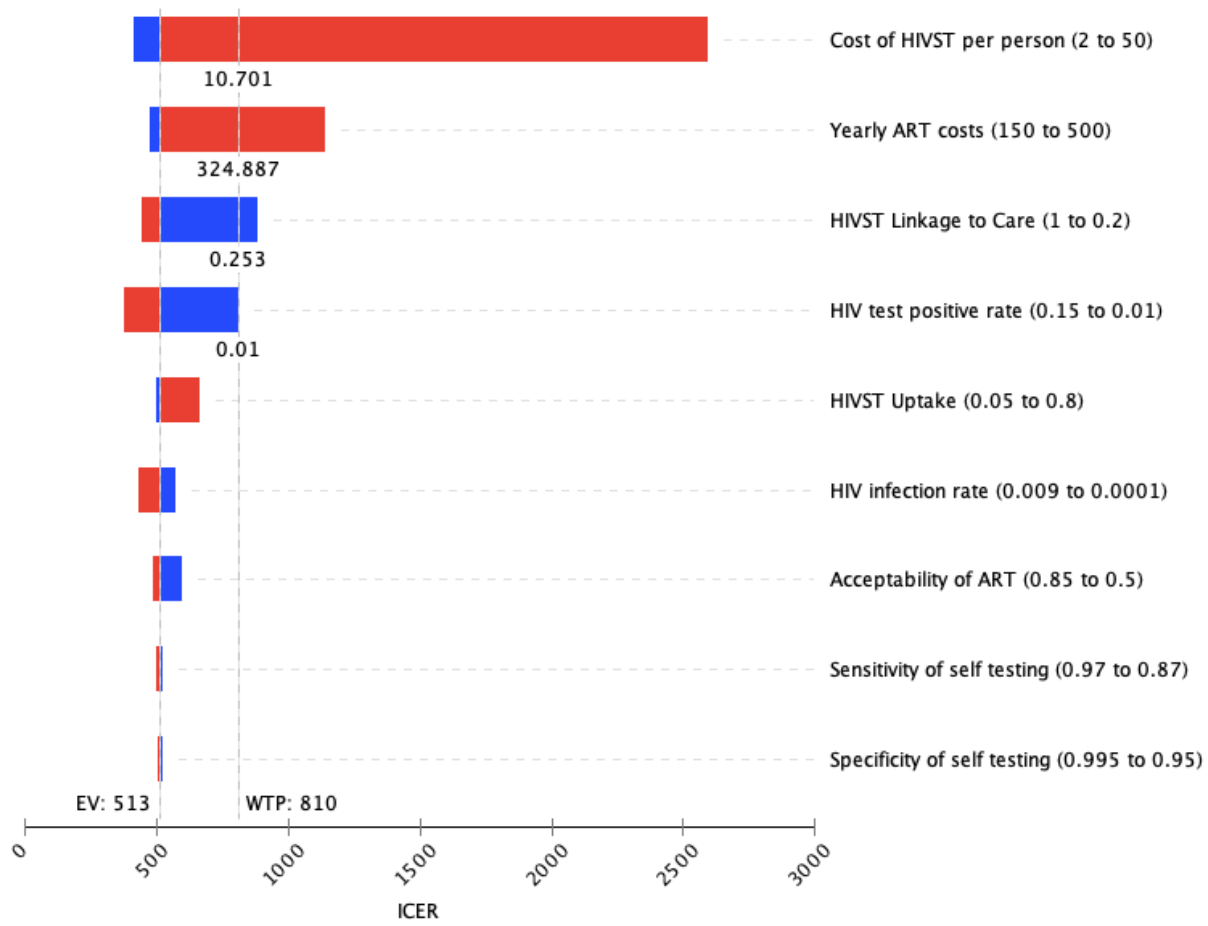
Figure Two (b): Decision Tree for HIV negative Markov state



HIVST, HIV self-testing; FBT, facility-based testing; AIDS, acquired immunodeficiency syndrome; ST, self-testing; ART, antiretroviral therapy

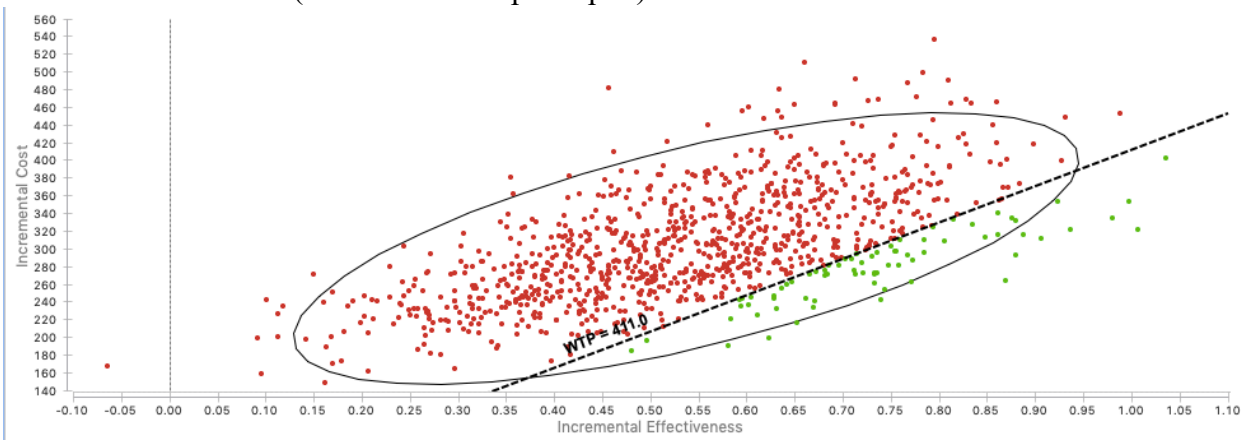
This diagram illustrates how individuals can move from the HIV negative stage to the HIV positive stage. In our base case scenario, on cycle 1, 5% of individuals entered the model in the HIV positive-untreated state. This represents the HIV test positive rate of the cohort. The other 95% of individuals entered the model in the HIV negative state. With every cycle there is a small probability of new HIV infection, where individuals who are HIV negative can move to the HIV positive-untreated state.

Figure Three: Deterministic Analysis of Base Case Scenario



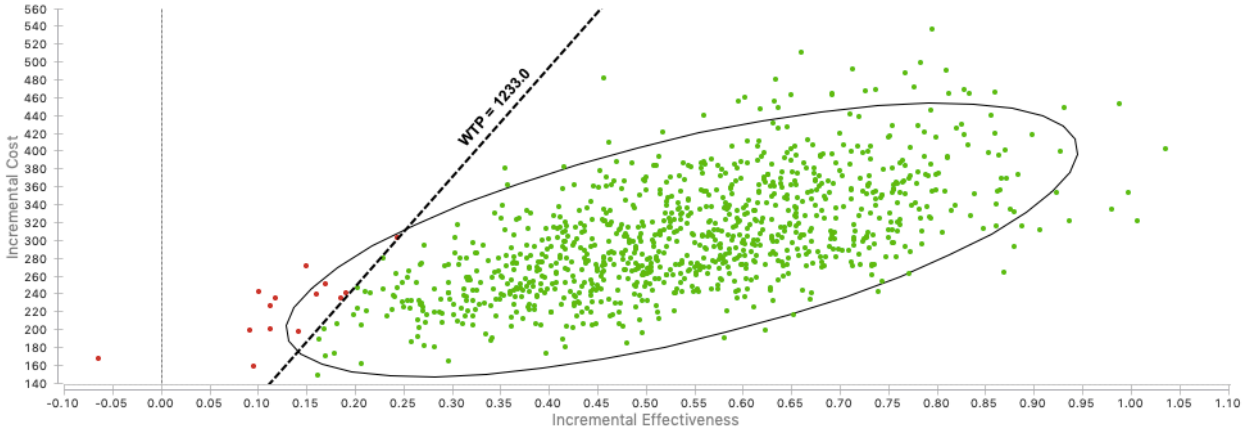
HIV ST, HIV self-test; ART, antiretroviral therapy

Figure Four: Probabilistic analysis for Malawi Community Based HIVST with a willingness to pay threshold of 411 USD (Malawian GDP per capita)



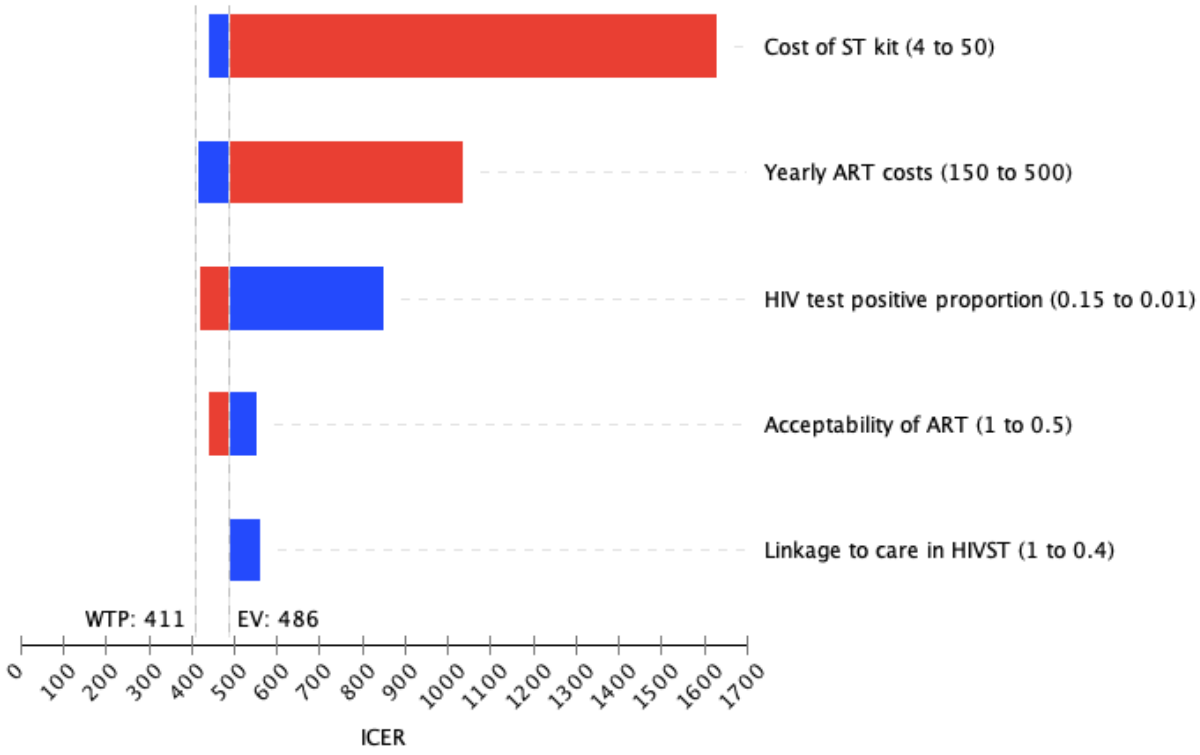
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US Dollars

Figure Five: Probabilistic analysis for Malawi Community Based HIVST with a willingness to pay threshold of 1233 USD (3x Malawian GDP per capita)



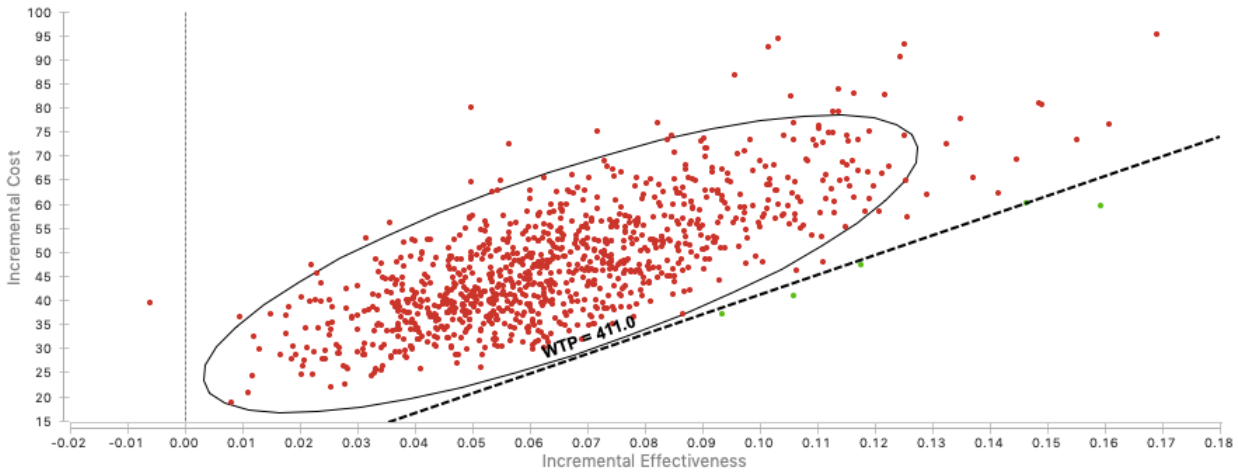
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US Dollars

Figure Six: Deterministic Analysis for Malawi Community Based HIVST



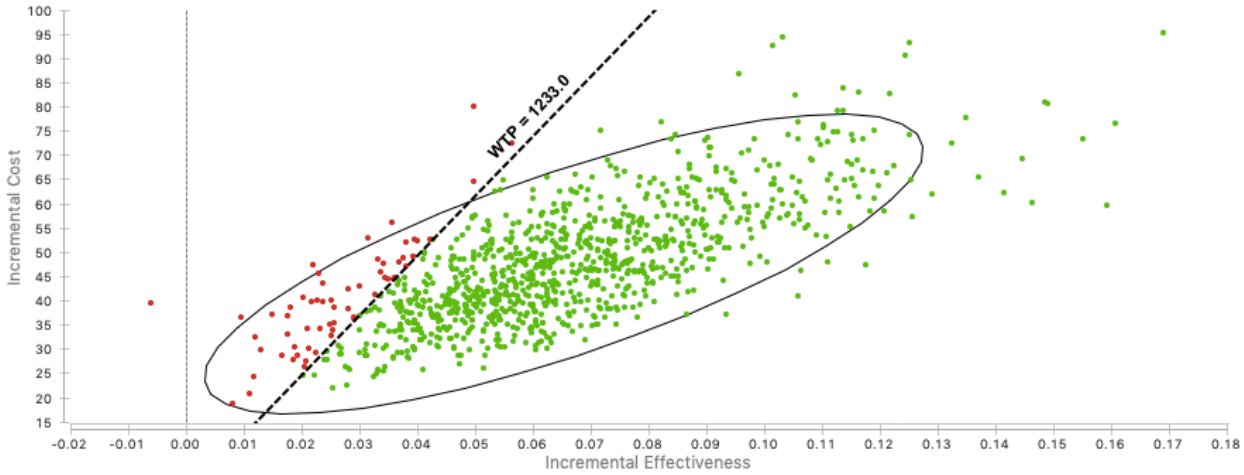
HIVST, HIV self-testing; ART, antiretroviral therapy

Figure Seven: Probabilistic analysis for Malawi Digital Based HIVST with a willingness to pay threshold of 411 USD (Malawian GDP per capita)



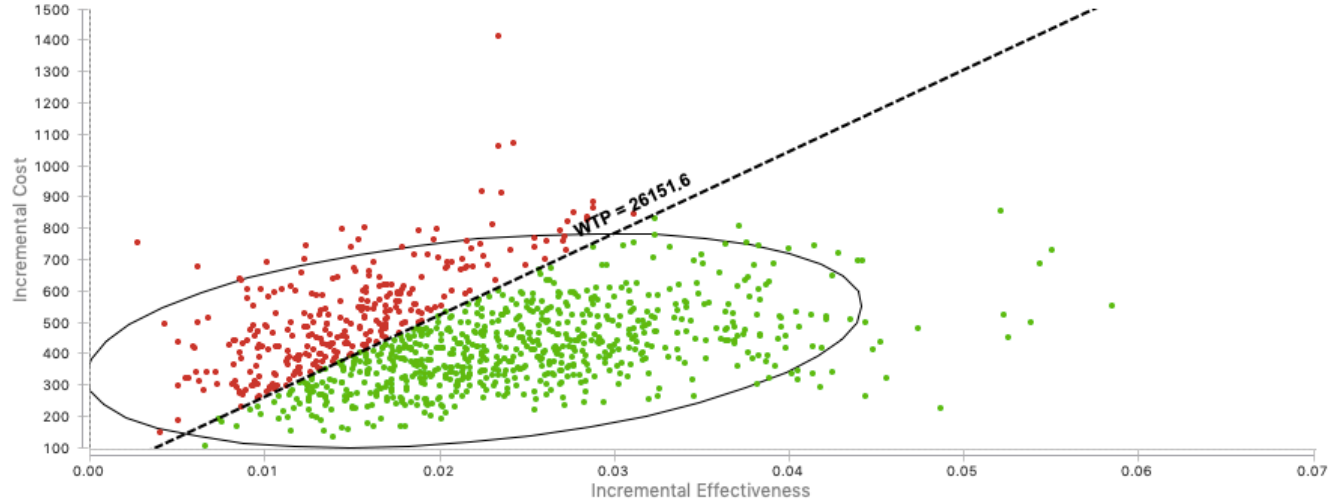
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Figure Eight: Probabilistic analysis for Malawi Digital Based HIVST with a willingness to pay threshold of 1233 USD (3x Malawian GDP per capita)



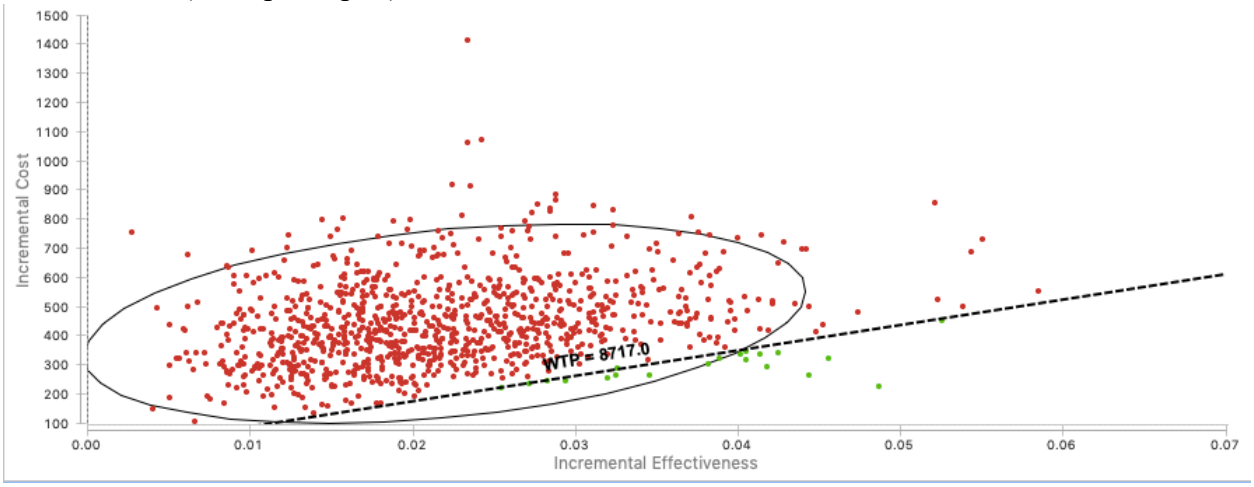
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Figure Nine: Probabilistic analysis for Brazil Community Based HIVST with a willingness to pay threshold of 26,151 USD (3x Brazilian GDP per capita)



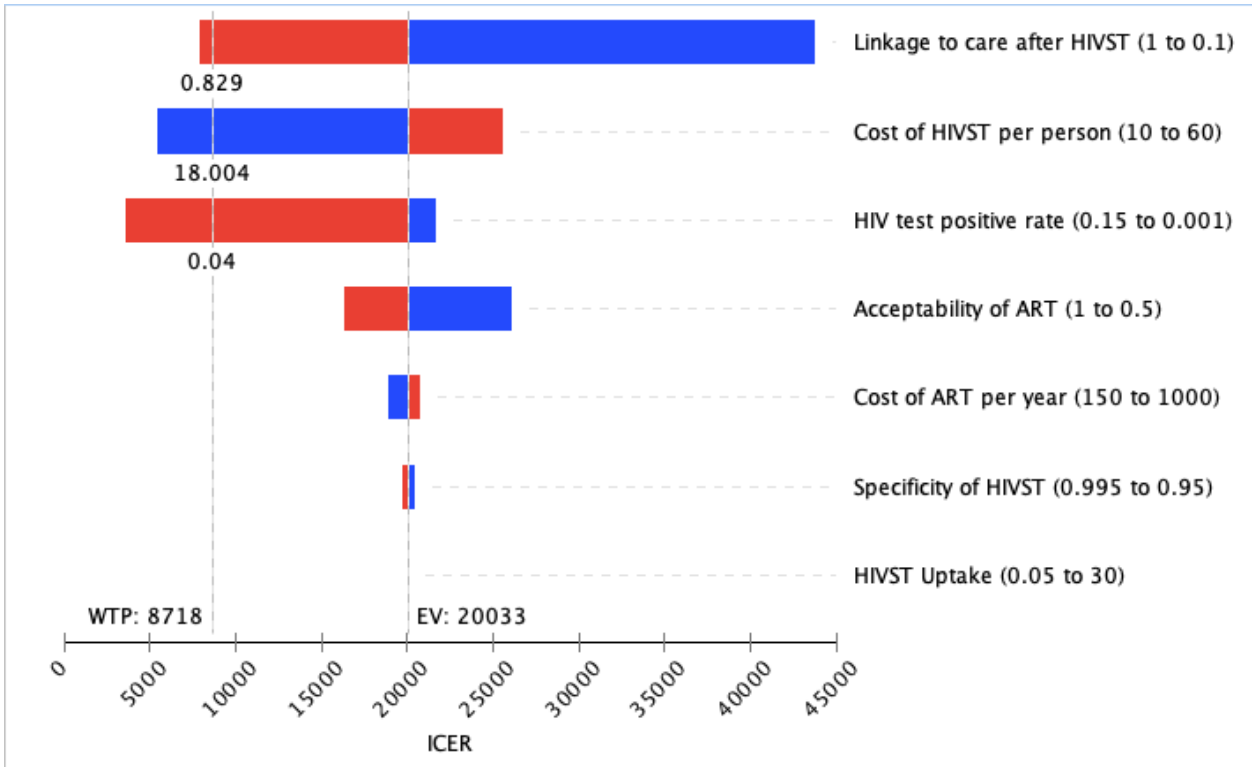
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Figure Ten: Probabilistic analysis for Brazil Community Based HIVST with a willingness to pay threshold of 8717 USD (GDP per capita)



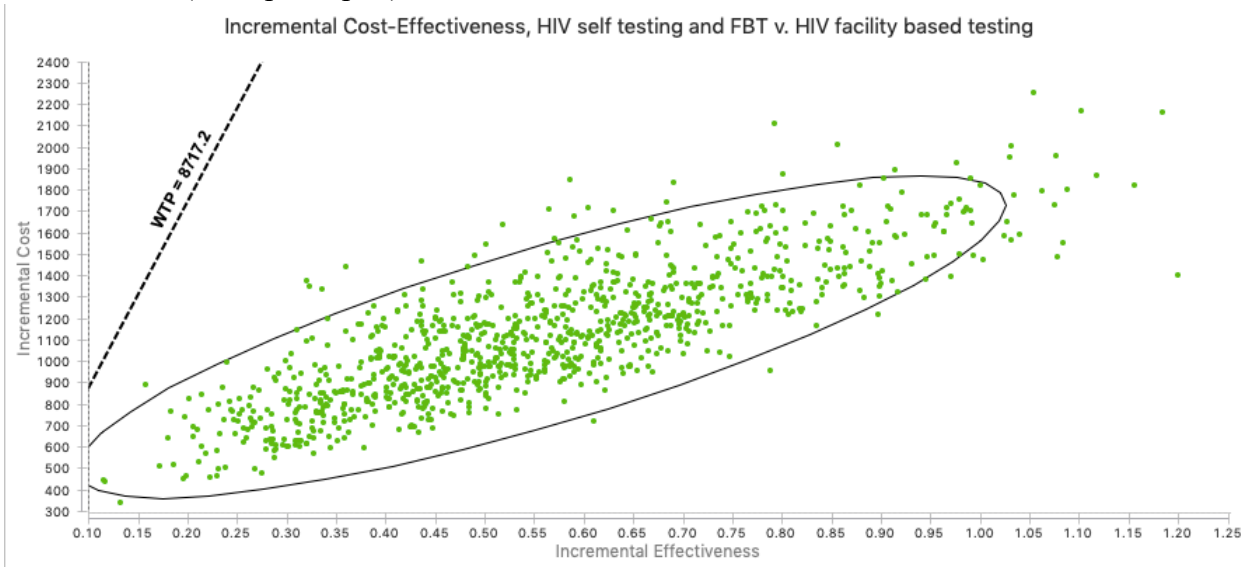
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Figure Eleven: Deterministic Analysis for HIVST in Brazil with Community Based HIVST



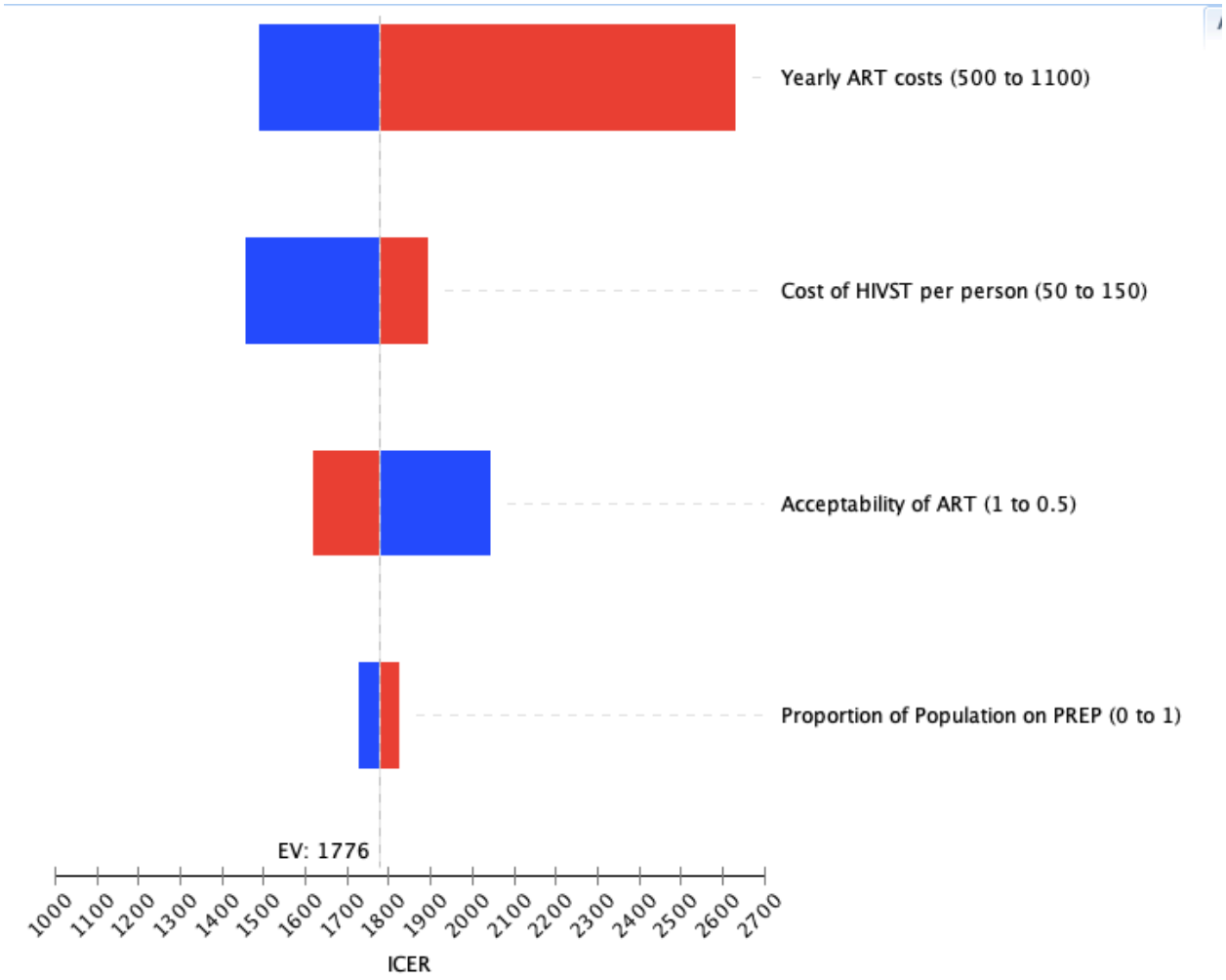
HIVST, HIV self-testing; ART, antiretroviral therapy

Figure Twelve: Probabilistic analysis for Brazil Digital based HIVST with a willingness to pay threshold of 8717 USD (GDP per capita)



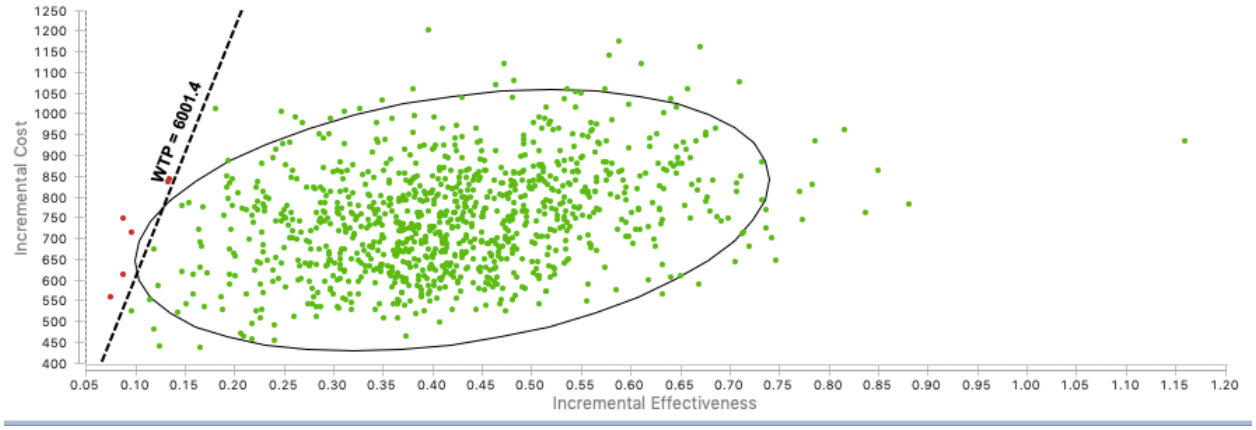
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Figure Thirteen: Deterministic analysis for Brazil Digital based HIVST among MSM with a willingness to pay threshold of 8717 USD (GDP per capita)



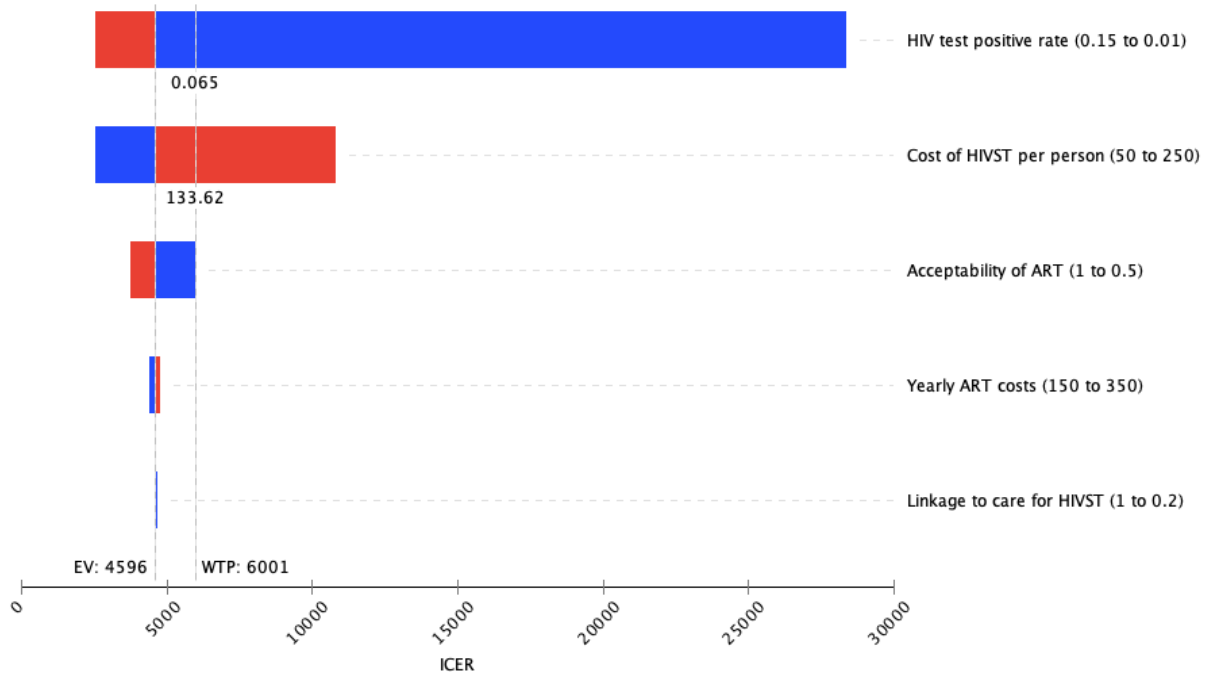
HIVST, HIV self-testing; ART, antiretroviral therapy; PREP, pre-exposure prophylaxis; MSM, men who have sex with men

Figure Fourteen: Probabilistic analysis for Brazil Digital based HIVST with a willingness to pay threshold of 8717 USD (GDP per capita)



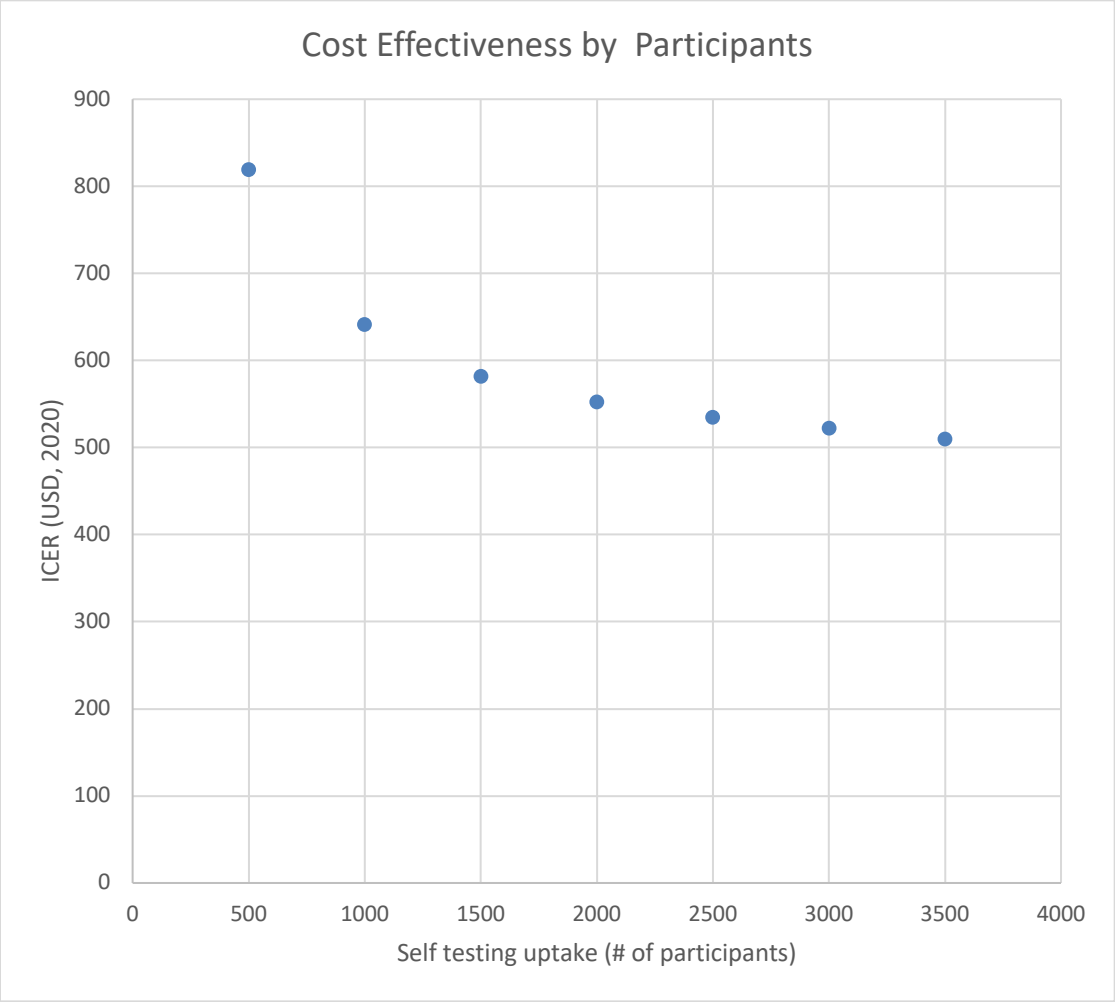
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Figure Fifteen: Deterministic Analysis of Digital Based HIVST in South Africa



HIVST, HIV self-testing; ART, antiretroviral therapy

Figure Sixteen: HIVST Cost Effectiveness by Increasing Uptake



HIVST, HIV self-testing; ICER, incremental cost effectiveness ratio; USD, US Dollars

Table One: Base Case Scenario Costs (USD, 2020)

Parameter	Point Estimate	Range
HIV self-test per person	$ 7[16, 21, 22, 39-43]	$ 5-9
Facility based test per person	$ 5[9, 11, 14, 38, 40, 50-53]	$3-7
ART (first year)	$188.67[54]	$150-800
ART (second year onwards)	$168.65[54]	$140-750
Self-testing uptake	0.1[9-14, 38-40, 49, 51, 55, 56]	0.05-0.8
Facility-based testing uptake	0.15[57]	0.1-0.35
Linkage to care (HIVST)	0.6[10, 11, 38, 51, 58, 59]	0.2-1
Acceptability of ART	0.75[9, 51, 53, 60-62]	0.5-0.9
HIV test positive rate	0.05[57]	0.01-0.15
HIVST (specificity)	0.979[51, 52, 63-65]	0.9-1
HIVST (sensitivity)	0.917[0, 50-53]	0.88-0.98

HIVST, HIV self-test; ART, antiretroviral therapy

Table Two (a): Emblematic Scenarios

	HIV test positive probability	HIV infection probability (per annum)[66]	Mortality probability (per annum)[67]	GDP per capita[34]
Malawi	0.09[13, 68, 69]	0.0029	0.006	410
Brazil	0.003[70, 71]	0.0022	0.00653	8717.2
South Africa	0.08[72, 73]	0.00034	0.009	6001.4
Thailand	0.005[66, 74, 75]	0.00007	0.007	7806.74

Table Two (b): Self-Testing Parameters for Emblematic Scenarios

Emblematic Scenario	HIV ST Cost (USD 2020 per ST)	CB/DB Intervention	HIVST Uptake (%)	Linkage to Care (%)	ART initiation (%)
South Africa-CB	37.7[10]	HIVST available through mobile testing units[7]	92[7]	50[7]	78.4[15, 76, 77]
South Africa-DB	99.58[15, 41]	Website promoting HIVST with online ordering[15]	21.4[15]	80[15]	78.4[6, 24, 60, 77]
Malawi- CB	11.38[13]	Volunteer delivery of HIVST to	100[13]	75[13]	58[13]

		homes within the community[13]			
Malawi- DB	11.45[40]	Text messages to general population promoting HIVST[12, 17, 18]	10.1[12, 17, 18]	85[12, 17, 18]	70[59, 62]
Brazil- CB	52.1[41]	HIVST available through mobile testing units[41]	49[41]	23[41]	80[42, 71, 78]
Brazil- DB	128[15, 41]	Website promoting HIVST with online ordering[15]	21.4[15]	80[15]	80[42, 71, 78]

CB, community-based; DB, digital-based; HIVST, HIV self-testing

This tables shows the inputs extracted from previously published literature that parameterized the model for our emblematic scenarios. For the Malawi community-based intervention, HIVST were delivered to all the homes within the community therefore the uptake was estimated at 100%.

Table Three: Cost Effectiveness Results for Base Case Scenario & Emblematic Scenarios

Base Case Scenario					
Strategy	Cost (USD, 2020)	Incremental Cost	Effectiveness (DALYs averted)	Incremental Effectiveness	ICER ($ per DALY averted)
HIV FBT	141	-	18.64	-	-
HIV ST + FBT	162	21	18.68	0.04	512.74
Malawi Community Based HIVST					
HIV FBT	151	-	25.3	-	-
HIV ST + FBT	497	339	26	0.7	485.71
Malawi Digital Based HIVST					
HIV FBT	168	-	17.27	-	-
HIV ST + FBT	218	49	17.35	0.07	673.70
Brazil Community Based HIVST					
HIV FBT	239	-	18.09	-	-
HIV ST + FBT	680	441	18.11	0.02	20032.83
Brazil Digital Based HIVST					
HIV FBT	1832	-	23.81	-	-

HIV ST + FBT	2872	1038	24.32	0.51	2028.09
Cost Effectiveness Results for Brazil Digital Based HIVST among MSM					
HIV FBT	4620	-	23.26	-	-
HIV ST + FBT	5784	1164	23.93	0.66	1756.89
Cost Effectiveness Results for South Africa Community Based HIVST					
HIV FBT	107	-	16.55	-	-
HIV ST + FBT	853	746	16.97	0.43	1753.67
Cost Effectiveness Results for South Africa Digital Based HIVST					
HIV FBT	153	-	16.9	-	-
HIV ST + FBT	547	395	17.07	0.09	4596.06

FBT, facility-based testing; HIV ST, HIV self-testing; USD, US dollars; DALY, disability adjusted life year; ICER, incremental cost effectiveness ratio; MSM, men who have sex with men

Appendices

Model Description:

For our intervention, we have modeled HIVST in addition to facility-based testing. In this scenario, there would be three possibilities, individuals who accept self-testing, individuals who accept conventional testing and those who do not accept both. Individuals who accept conventional testing would go through a process similar to what is described in the previous paragraph. Individuals who would accept HIV self-testing, will screen either positive or negative. If positive, they would be offered confirmatory testing at a health care facility. Once confirmed positive, they will be counseled on ART therapy and would be started if accepted. Individuals who are lost to follow up before diagnostic testing would go into the HIV positive, untreated Markov state. Those who are confirmed to have HIV but do not accept ART initiation will go into the HIV positive, diagnosed but untreated Markov state.

Our reference strategy is facility base testing scenario, where individuals who choose to be tested would self-present to a facility offering HIV testing and would be offered the conventional rapid HIV test (finger-prick). If positive, they would be offered a confirmatory rapid test (finger-prick). In case of discordant results, an ELISA would be performed. Once confirmed positive, they would be provided with

counselling and ART therapy would be initiated if accepted by the patient. Individuals who are lost to follow-up or do not accept ART initiation will go into the HIV positive, diagnosed but untreated Markov state.

The death rate was country specific and included for all Markov states, based on the general population mortality sourced from the World Bank database[67]. The exception to this was the death rate for AIDS, which was higher than that of the general population and based on published studies[79-81].

Key Model Assumptions:

There are several important assumptions embedded within the model structure. We assumed that all individuals entering the model had an equal probability of testing positive and that the test positivity rate was constant over the model horizon. There was a lack of literature in terms of the impact of HIVST on long term ART adherence. We extrapolated ART acceptability and adherence based on facility-based studies and applied this to the HIVST scenario.

For each cycle the population has a probability of accepting ST or FBT but given the decision tree structure the testing options are mutually exclusive. Therefore, our model cannot account for individuals who may test multiple times per year or test using both ST and FBT approaches. We assumed that previous HIV testing would not impact risk taking behavior or modify the risk of new HIV infection.

This model does not include HIV transmission or the epidemiological impact of HIVST on the underlying prevalence of HIV within the community, therefore the underlying HIV test positivity rate remains constant over the thirty- year cycle. If HIVST decreases the prevalence of HIV within a community, then our model will underestimate the cost effectiveness as it will not account for reduced transmission over time.

<u>Emblematic Scenario: Thailand</u>

Community Based

The community-based intervention in Thailand was based on an intervention conducted in Vietnam where

peer educators provided outreach services including HIVST, targeting high risk populations[82]. Peer educators then conducted post-test counselling and assisted with linkage to care and ART initiation. Overall uptake of HIV testing was not collected in this study, but 22.4% of individuals opted for HIVST (versus FBT). Rates of linkage to care and ART initiation were high, 97 and 94% respectively.

This study did not include costs, and no studies were identified in our previous literature review that included costs that evaluated self-testing in Asia. We therefore used unit costs of the OraQuick HIVST[27] and added the average proportion of implementation costs, based on our separately published systematic review.

Using extrapolated cost inputs and efficacy data from the above study, our model predicts that HIVST with a digital based intervention would be, on average, highly cost effective at an ICER of 4248.26 USD per DALY averted with a WTP threshold of 7806.74 USD (appendix table 1). This should be interpreted with caution given the large uncertainty around cost estimates used in this scenario. Probabilistic analysis shows that the intervention would be cost effective in 93% of the scenarios run (figure 16).

Digital Based:

We modeled the digital based intervention based on uptake and linkage to care inputs from a study conducted in Thailand that used online resources to promote HIVST among the MSM population [83]. Men were allowed to self-select facility or web based HIVST including pre and post testing counselling. HIV ST done at home had the option to be supervised by a health worker via video chat. Rates of linkage to care and ART initiation were 75% and 52.8% respectively. Using extrapolated cost inputs and efficacy data from the above study, our model predicts that HIVST with a digital based intervention would be on average cost effective at an ICER of 4769.9 USD per DALY averted with a WTP threshold of 7806.74 USD (appendix table 1). Probabilistic analysis shows that the intervention would be cost effective in 55% of the scenarios run (figure 17).

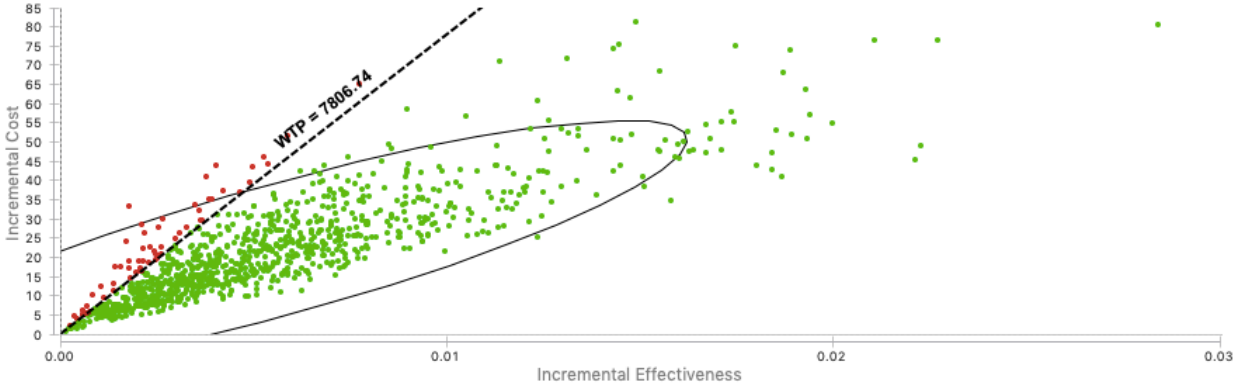
Deterministic analysis indicates that the main drivers of cost effectiveness within this scenario would be

HIV test positive rate, linkage to care and cost of HIV self-testing (figure 18). HIVST was cost effective with a test positive rate above 0.3%, linkage to care above 36% and HIVST uptake under 73%.

Appendix Table One

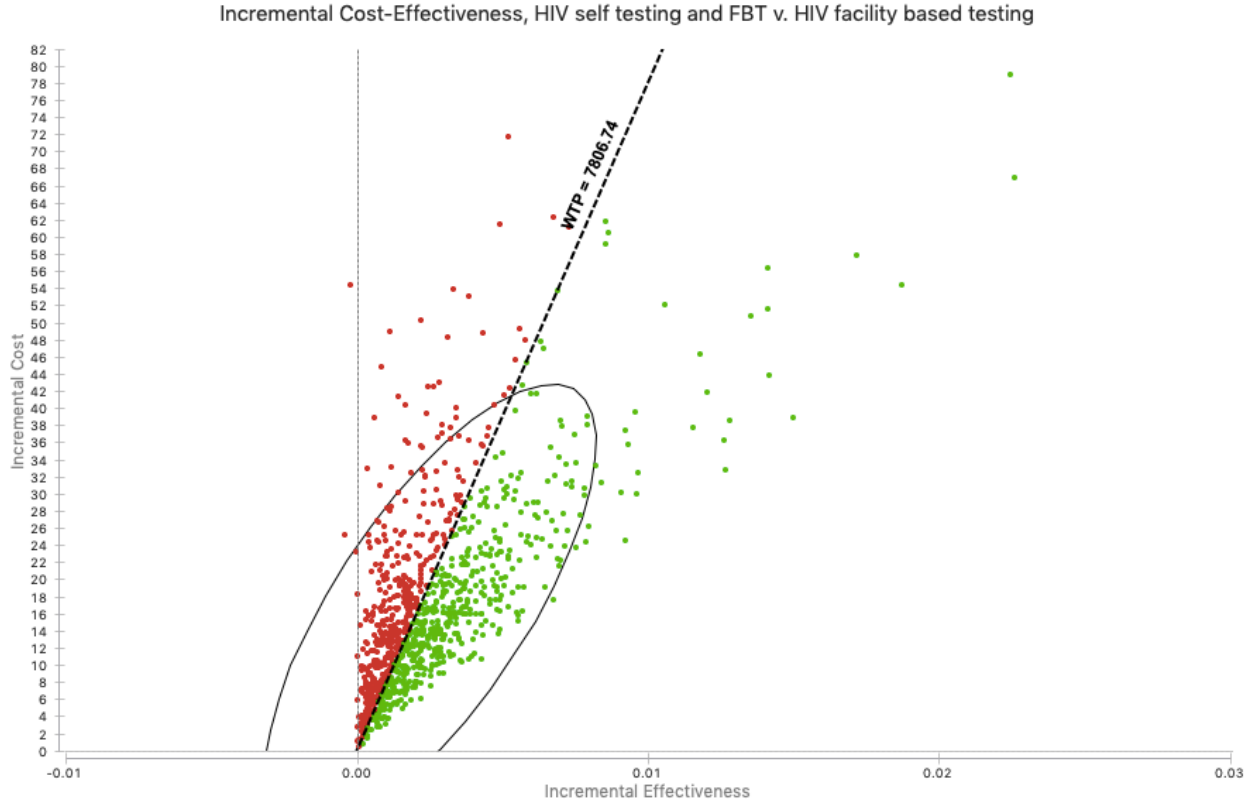
Cost Effectiveness Results for Thailand Community Based HIVST					
HIV FBT	202	-	19.29	-	-
HIV ST + FBT	223	21	19.295	0.005	4248.26
Cost Effectiveness Results for Thailand Digital Based HIVST					
HIV FBT	202	-	19.29	-	-
HIV ST + FBT	221	19	19.294	0.004	4769.90

Appendix Figure One: Probabilistic analysis for Thailand Community Based HIVST with a willingness to pay threshold of 7807 USD (GDP per capita)



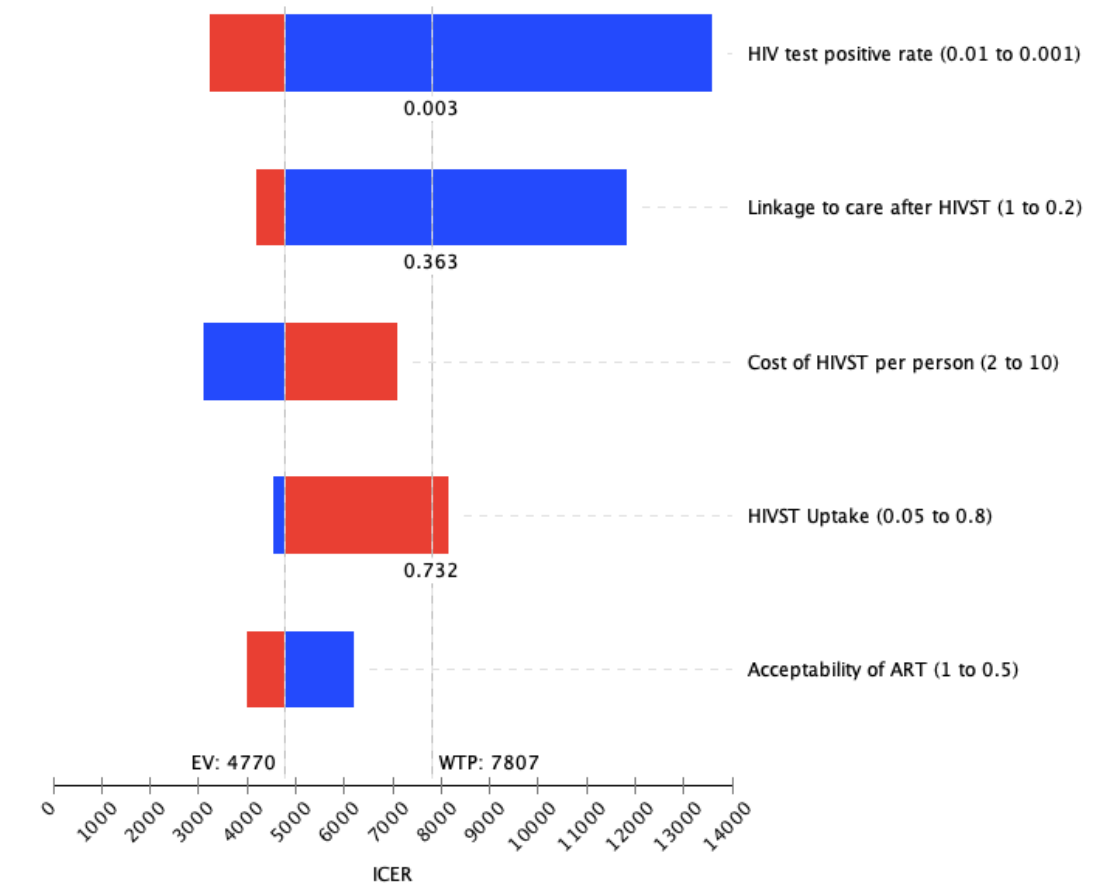
HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Appendix Figure Two: Probabilistic analysis for Thailand Digital Based HIVST with a willingness to pay threshold of 7807 USD (GDP per capita)



HIVST, HIV self-testing; GDP, gross domestic product; WTP, willingness to pay threshold; USD, US dollars

Appendix Figure 3: Deterministic Analysis of Digital Based HIVST in Thailand



HIVST, HIV self-testing; ART, antiretroviral therapy

References

1. Van Hout MC, Stover H, Benamara K, Bauer P, Salah E. 90-90-90: catalysing the response to HIV by enhancing prison visibility in the Joint United Nations Programme on HIV and AIDS (UNAIDS) strategy beyond 2021. Public Health. 2021;190: e5-e6.
2. Fuente-Soro L, Lopez-Varela E, Augusto O, et al. Monitoring progress towards the first UNAIDS target: understanding the impact of people living with HIV who re-test during HIV-testing campaigns in rural Mozambique. J Int AIDS Soc. 2018;21: e25095.
3. Ssekalembe G, Isfandiari MA, Suprianto H. Current Status Towards 90-90-90 UNAIDS Target and Factors Associated with HIV Viral Load Suppression in Kediri City, Indonesia. HIV AIDS (Auckl). 2020;12: 47-57.
4. de Mendoza C. UNAIDS Update Global HIV Numbers. AIDS Rev. 2019;21: 170-171.
5. Frost LJ, Reich MR. Creating access to health technologies in poor countries. Health Aff (Millwood). 2009;28: 962-973.
6. Krause J, Subklew-Sehume F, Kenyon C, Colebunders R. Acceptability of HIV self-testing: a systematic literature review. BMC Public Health. 2013;13: 735.
7. Pettifor A, Lippman SA, Kimaru L, et al. HIV self-testing among young women in rural South Africa: A randomized controlled trial comparing clinic-based HIV testing to the choice of either clinic testing or HIV self-testing with secondary distribution to peers and partners. EClinicalMedicine. 2020;21: 100327.
8. Hubbard SJ, Ma M, Wahnich A, Clarke A, Myers JE, Saleh LD. #Testathome: Implementing 2 Phases of a HIV Self-Testing Program Through Community-Based Organization Partnerships in New York City. Sex Transm Dis. 2020;47: S48-S52.
9. Maheswaran H, Clarke A, MacPherson P, et al. Cost-Effectiveness of Community-based Human Immunodeficiency Virus Self-Testing in Blantyre, Malawi. Clin Infect Dis. 2018;66: 1211-1221.
10. d'Elbee M, Makhetha MC, Jubilee M, et al. Using HIV self-testing to increase the affordability of community-based HIV testing services. AIDS. 2020;34: 2115-2123.
11. Cambiano V, Johnson CC, Hatzold K, et al. The impact and cost-effectiveness of community-based HIV self-testing in sub-Saharan Africa: a health economic and modelling analysis. J Int AIDS Soc. 2019;22 Suppl 1: e25243.
12. Kelvin EA, George G, Kinyanjui S, et al. Announcing the availability of oral HIV self-test kits via text message to increase HIV testing among hard-to-reach truckers in Kenya: a randomized controlled trial. BMC public health. 2019;19: 7.
13. Indravudh PP, Fielding K, Kumwenda MK, et al. Effect of community-led delivery of HIV self-testing on HIV testing and antiretroviral therapy initiation in Malawi: A cluster-randomised trial. PLoS Med. 2021;18: e1003608.
14. Mangenah C, Mwenge L, Sande L, et al. Economic cost analysis of door-to-door community-based distribution of HIV self-test kits in Malawi, Zambia and Zimbabwe. J Int AIDS Soc. 2019;22 Suppl 1: e25255.
15. De Boni RB, Veloso VG, Fernandes NM, et al. An Internet-Based HIV Self-Testing Program to Increase HIV Testing Uptake Among Men Who Have Sex With Men in Brazil: Descriptive Cross-Sectional Analysis. J Med Internet Res. 2019;21: e14145.
16. Pant Pai N, Sharma J, Shivkumar S, et al. Supervised and unsupervised self-testing for HIV in high- and low-risk populations: a systematic review. PLoS Med. 2013;10: e1001414.
17. Kelvin EA, George G, Mwai E, et al. Offering Self-administered Oral HIV Testing as a Choice to Truck Drivers in Kenya: Predictors of Uptake and Need for Guidance While Self-testing. AIDS Behav. 2018;22: 580-592.

18. Kelvin EA, George G, Mwai E, et al. A Randomized Controlled Trial to Increase HIV Testing Demand Among Female Sex Workers in Kenya Through Announcing the Availability of HIV Self-testing Via Text Message. AIDS Behav. 2019;23: 116-125.
19. Wesolowski L, Chavez P, Sullivan P, et al. Distribution of HIV Self-tests by HIV-Positive Men Who Have Sex with Men to Social and Sexual Contacts. AIDS Behav. 2019;23: 893-899.
20. Chanda MM, Ortblad KF, Mwale M, et al. HIV self-testing among female sex workers in Zambia: A cluster randomized controlled trial. PLoS Med. 2017;14: e1002442.
21. Jamil MS, Guy RJ, Bavinton BR, et al. HIV testing self-efficacy is associated with higher HIV testing frequency and perceived likelihood to self-test among gay and bisexual men. Sex Health. 2017;14: 170-178.
22. Reddick CG, Enriquez R, Harris RJ, Sharma B. Determinants of broadband access and affordability: An analysis of a community survey on the digital divide. Cities. 2020;106: 102904.
23. Qin Y, Han L, Babbitt A, et al. Experiences using and organizing HIV self-testing. AIDS. 2018;32: 371-381.
24. McGuire M, de Waal A, Karellis A, et al. HIV self-testing with digital supports as the new paradigm: A systematic review of global evidence (2010-2021). EClinicalMedicine. 2021;39: 101059.
25. TreeAge Pro 2021, R1. TreeAge Software, Williamstown, MA; software available at http://www.treeage.com.
26. Zelin J, Garrett N, Saunders J, et al. An evaluation of the performance of OraQuick ADVANCE Rapid HIV-1/2 Test in a high-risk population attending genitourinary medicine clinics in East London, UK. Int J STD AIDS. 2008;19: 665-667.
27. Technologies. O. OraQuick HIV Self Tests. Available from URL: https://www.orasure.com/products-infectious/OraQuick-Self-Test.html [accessed July 4, 2021.
28. Holguin A, Gutierrez M, Portocarrero N, Rivas P, Baquero M. Performance of OraQuick Advance Rapid HIV-1/2 Antibody Test for detection of antibodies in oral fluid and serum/plasma in HIV-1+ subjects carrying different HIV-1 subtypes and recombinant variants. J Clin Virol. 2009;45: 150-152.
29. O'Connell RJ, Merritt TM, Malia JA, et al. Performance of the OraQuick rapid antibody test for diagnosis of human immunodeficiency virus type 1 infection in patients with various levels of exposure to highly active antiretroviral therapy. J Clin Microbiol. 2003;41: 2153-2155.
30. Watson V, Dacombe RJ, Williams C, et al. Re-reading of OraQuick HIV-1/2 rapid antibody test results: quality assurance implications for HIV self-testing programmes. J Int AIDS Soc. 2019;22 Suppl 1: e25234.
31. Luz PM, Osher B, Grinsztejn B, et al. The cost-effectiveness of HIV pre-exposure prophylaxis in men who have sex with men and transgender women at high risk of HIV infection in Brazil. J Int AIDS Soc. 2018;21: e25096.
32. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396: 1204-1222.
33. Bertram MY, Lauer JA, Stenberg K, Edejer TTT. Methods for the Economic Evaluation of Health Care Interventions for Priority Setting in the Health System: An Update From WHO CHOICE. Int J Health Policy Manag. 2021.
34. World Bank (2020). GDP per capita: current USD. Retrieved July 11, 2021 from https://data.worldbank.org/indicator/NY.GDP.PCAP.CD.
35. World Bank. 2021. Official Exchange Rate. Retrieved August 1, 2021 from https://data.worldbank.org/indicator/PA.NUS.FCRF.
36. World Bank. 2021. Inflation, consumer prices (%). Retrieved August 13, 2021 from https://data.worldbank.org/indicator/FP.CPI.TOTL.ZG.

37. Bank of Canada. 2021. Inflation Calculator. Retrieved August 31, 2021 from https://www.bankofcanada.ca/rates/related/inflation-calculator/.
38. Cambiano V, Ford D, Mabugu T, et al. Assessment of the Potential Impact and Cost-effectiveness of Self-Testing for HIV in Low-Income Countries. J Infect Dis. 2015;212: 570-577.
39. Bulterys MA, Mujugira A, Nakyanzi A, et al. Costs of Providing HIV Self-Test Kits to Pregnant Women Living with HIV for Secondary Distribution to Male Partners in Uganda. Diagnostics (Basel). 2020;10.
40. George G, Chetty T, Strauss M, et al. Costing analysis of an SMS-based intervention to promote HIV self-testing amongst truckers and sex workers in Kenya. PLoS One. 2018;13: e0197305.
41. da Cruz MM, Cota VL, Lentini N, et al. Comprehensive approach to HIV/AIDS testing and linkage to treatment among men who have sex with men in Curitiba, Brazil. PLoS One. 2021;16: e0249877.
42. Brazil Go. Relatório de monitoramento clínico do HIV2017.
43. Dimitrov D, Wood D, Ulrich A, et al. Projected effectiveness of HIV detection during early infection and rapid ART initiation among MSM and transgender women in Peru: A modeling study. Infectious Disease Modelling. 2019;4: 73-82.
44. Kerr L, Kendall C, Guimaraes MDC, et al. HIV prevalence among men who have sex with men in Brazil: results of the 2nd national survey using respondent-driven sampling. Medicine (Baltimore). 2018;97: S9-S15.
45. Teixeira SLM, Jalil CM, Jalil EM, et al. Evidence of an untamed HIV epidemic among MSM and TGW in Rio de Janeiro, Brazil: a 2018 to 2020 cross-sectional study using recent infection testing. Journal of the International AIDS Society. 2021;24: e25743.
46. Veronese V, Ryan KE, Hughes C, Lim MS, Pedrana A, Stoove M. Using Digital Communication Technology to Increase HIV Testing Among Men Who Have Sex With Men and Transgender Women: Systematic Review and Meta-Analysis. J Med Internet Res. 2020;22: e14230.
47. Cameron D, Ubels J, Norstrom F. On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review. Glob Health Action. 2018;11: 1447828.
48. McDougall JA, Furnback WE, Wang BCM, Mahlich J. Understanding the global measurement of willingness to pay in health. J Mark Access Health Policy. 2020;8: 1717030.
49. Njau B, Damian DJ, Abdullahi L, Boulle A, Mathews C. The effects of HIV self-testing on the uptake of HIV testing, linkage to antiretroviral treatment and social harms among adults in Africa: A systematic review and meta-analysis. PLoS One. 2021;16: e0245498.
50. Zachary D, Mwenge L, Muyoyeta M, et al. Field comparison of OraQuick ADVANCE Rapid HIV-1/2 antibody test and two blood-based rapid HIV antibody tests in Zambia. BMC Infect Dis. 2012;12: 183.
51. Choko AT, Corbett EL, Stallard N, et al. HIV self-testing alone or with additional interventions, including financial incentives, and linkage to care or prevention among male partners of antenatal care clinic attendees in Malawi: An adaptive multi-arm, multi-stage cluster randomised trial. PLoS Med. 2019;16: e1002719.
52. Choko AT, Desmond N, Webb EL, et al. The uptake and accuracy of oral kits for HIV self-testing in high HIV prevalence setting: a cross-sectional feasibility study in Blantyre, Malawi. PLoS Med. 2011;8: e1001102.
53. Maheswaran H, Barton P. Intensive case finding and isoniazid preventative therapy in HIV infected individuals in Africa: economic model and value of information analysis. PLoS One. 2012;7: e30457.
54. Sarkar S, Corso P, Ebrahim-Zadeh S, Kim P, Charania S, Wall K. Cost-effectiveness of HIV Prevention Interventions in Sub-Saharan Africa: A Systematic Review. EClinicalMedicine. 2019;10: 10-31.
55. Nichols BE, Offorjebe OA, Cele R, et al. Economic evaluation of facility-based HIV self-testing among adult outpatients in Malawi. J Int AIDS Soc. 2020;23: e25612.

56. Dovel K, Shaba F, Offorjebe OA, et al. Effect of facility-based HIV self-testing on uptake of testing among outpatients in Malawi: a cluster-randomised trial. Lancet Glob Health. 2020;8: e276-e287.
57. Organization WH. The Global Health Observatory: HIV Testing and Diagnosis2019.
58. Sibanda EL, McCoy SI. Secondary distribution of HIV self-tests improves coverage. Lancet HIV. 2020;7: e732-e733.
59. Rivera AS, Hernandez R, Mag-Usara R, et al. Implementation outcomes of HIV self-testing in low- and middle- income countries: A scoping review. PLoS One. 2021;16: e0250434.
60. Garrett N, Norman E, Leask K, et al. Acceptability of Early Antiretroviral Therapy Among South African Women. AIDS Behav. 2018;22: 1018-1024.
61. Kumwenda MK, Johnson CC, Choko AT, et al. Exploring social harms during distribution of HIV self-testing kits using mixed-methods approaches in Malawi. J Int AIDS Soc. 2019;22 Suppl 1: e25251.
62. Hatzold K, Gudukeya S, Mutseta MN, et al. HIV self-testing: breaking the barriers to uptake of testing among men and adolescents in sub-Saharan Africa, experiences from STAR demonstration projects in Malawi, Zambia and Zimbabwe. J Int AIDS Soc. 2019;22 Suppl 1: e25244.
63. Stevens DR, Vrana CJ, Dlin RE, Korte JE. A Global Review of HIV Self-testing: Themes and Implications. AIDS Behav. 2018;22: 497-512.
64. Choko AT, MacPherson P, Webb EL, et al. Uptake, Accuracy, Safety, and Linkage into Care over Two Years of Promoting Annual Self-Testing for HIV in Blantyre, Malawi: A Community-Based Prospective Study. PLoS Med. 2015;12: e1001873.
65. Marley G, Kang D, Wilson EC, et al. Introducing rapid oral-fluid HIV testing among high risk populations in Shandong, China: feasibility and challenges. BMC public health. 2014;14: 422.
66. UNAIDS. 2021. New HIV Infections. Retrieved July 11, 2021 from https://aidsinfo.unaids.org.
67. DataBank WB. Death Rate, crude per 1,000 people 2020.
68. Mwenge L, Sande L, Mangenah C, et al. Costs of facility-based HIV testing in Malawi, Zambia and Zimbabwe. PLoS One. 2017;12: e0185740.
69. Burke RM, Henrion MYR, Mallewa J, et al. Incidence of HIV-positive admission and inpatient mortality in Malawi [2012-2019]: a population cohort study. AIDS. 2021.
70. Grinberg G, Giron LB, Knoll RK, et al. High prevalence and incidence of HIV-1 in a counseling and testing center in the city of Itajai, Brazil. Braz J Infect Dis. 2015;19: 631-635.
71. Melo MC, Almeida VC, Donalisio MR. Trend incidence of HIV-AIDS according to different diagnostic criteria in Campinas-SP, Brazil from 1980 to 2016. Cien Saude Colet. 2021;26: 297-307.
72. Akullian A, Vandormael A, Miller JC, et al. Large age shifts in HIV-1 incidence patterns in KwaZulu-Natal, South Africa. Proc Natl Acad Sci U S A. 2021;118.
73. Barnighausen T, Wallrauch C, Welte A, et al. HIV incidence in rural South Africa: comparison of estimates from longitudinal surveillance and cross-sectional cBED assay testing. PLoS One. 2008;3: e3640.
74. Park LS, Siraprapasiri T, Peerapatanapokin W, Manne J, Niccolai L, Kunanusont C. HIV transmission rates in Thailand: evidence of HIV prevention and transmission decline. J Acquir Immune Defic Syndr. 2010;54: 430-436.
75. Kawichai S, Celentano DD, Vongchak T, et al. HIV voluntary counseling and testing and HIV incidence in male injecting drug users in northern Thailand: evidence of an urgent need for HIV prevention. J Acquir Immune Defic Syndr. 2006;41: 186-193.
76. Hamilton A, Thompson N, Choko AT, et al. HIV Self-Testing Uptake and Intervention Strategies Among Men in Sub-Saharan Africa: A Systematic Review. Front Public Health. 2021;9: 594298.
77. Johnson CC, Kennedy C, Fonner V, et al. Examining the effects of HIV self-testing compared to standard HIV testing services: a systematic review and meta-analysis. J Int AIDS Soc. 2017;20: 21594.

78. de Sousa ACL, Eleuterio TA, Coutinho JVA, Guimaraes RM. Assessing antiretroviral therapy success in HIV/AIDS morbidity and mortality trends in Brazil, 1990-2017: an interrupted time series study. Int J STD AIDS. 2021;32: 127-134.
79. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013;41: 140-156.
80. Mindel A, Tenant-Flowers M. ABC of AIDS: Natural history and management of early HIV infection. BMJ. 2001;322: 1290-1293.
81. Vellozzi C, Brooks JT, Bush TJ, et al. The study to understand the natural history of HIV and AIDS in the era of effective therapy (SUN Study). Am J Epidemiol. 2009;169: 642-652.
82. Nguyen VTT, Phan HT, Kato M, et al. Community-led HIV testing services including HIV self-testing and assisted partner notification services in Vietnam: lessons from a pilot study in a concentrated epidemic setting. J Int AIDS Soc. 2019;22 Suppl 3: e25301.
83. Phanuphak N, Jantarapakde J, Himmad L, et al. Linkages to HIV confirmatory testing and antiretroviral therapy after online, supervised, HIV self-testing among Thai men who have sex with men and transgender women. J Int AIDS Soc. 2020;23: e25448.

Conclusion

The three components of my thesis contain common themes and implications for scale up of systematic screening and HIVST. The cost effectiveness of both systematic screening and HIVST were highly context dependent. The key drivers of cost effectiveness for systematic screening in TB were very similar to the key drivers of cost effectiveness for HIVST. These included underlying test positivity rates in the population eligible for testing, unit costs and programmatic costs.

Strengths & Weaknesses

The major strength of this thesis is the complementary nature of the first two chapters that went on to inform the economic model. The literature reviews are comprehensive and by using the data from the review to inform the economic model, we were able to ensure that the model reflects the most up to date and current evidence around HIVST. Instead of using a single database to inform the model inputs, we have used averages from the systematic review along with the range of published values which were varied by deterministic analysis. The model is adaptable across many contexts which increases its practicality and potential for real world use in HIVST implementation. The model is the first economic model published to include PrEP use, which reflects the increasing uptake of PrEP among high-risk populations particularly in middle income settings. We are also the first to publish a model that evaluates the cost utility of digital and community-based programs to support HIVST. This is particularly relevant as they could mediate the major disadvantage of HIVST, which is increased loss to follow up.

The systematic reviews are both weakened by the potential for publication bias. It is likely that studies that found that systematic screening and HIVST were not cost effectiveness were less likely to be published. This may skew our data into overestimating the cost effectiveness of

systematic screening andHIVST.

The economic model has limitations. Firstly, it does not account for the impact of HIVST on the underlying community prevalence of HIV. If HIVST decreases the community test positive rates of HIV, the model will underestimate the cost effectiveness of HIVST as it does not include any transmission modeling. The cost of HIV diagnostics and treatment change rapidly, which will require regular updating of the model inputs in order to continue to produce accurate cost effectiveness estimates. We used the DALY averted as our primary outcome measure. The DALY averted is an aggregate measure of years of life lost (YLL) and years of life disabled (YLD) (time disabled multiplied by a disability weight) to produce a discrete value between 0-1[53, 54]. The disability weights used in the model were sourced from the Global Burden of Disease study and are meant to be used universally across different countries and cultures[1]. There is subjectivity and nuance around a culture or person's view and valuation of disability which challenges the notion that an absolute value that can be associated with a disease state. Admittedly, I feel that it is inherently flawed to summarize the complex and personal experience of health and illness into a universal value. Despite these factors we used DALYs averted because they included both the quantity and quality of life affected by HIVST. Our model is meant to be used on a population level and DALYs averted are a useful outcome measure to summarize the aggregate loss of health within a population. DALYs averted are the utility measure most commonly used in global health economics, and they allow for generalizability between studies. It is important to interpret the findings of this model through a human lens and remember that the outcome measures used were imperfect and cannot capture the full picture of human health and illness.

For both the systematic reviews and the model there was a paucity of data around costs that were incurred by patients. All of the studies identified reported health system incurred costs, therefore

the model is only able to estimate cost effectiveness from the perspective of the health system. In the future, more emphasison patient incurred costs would be important. The impact of systematic screening and HIVST on factors like patient time and loss of productivity remain unknown.

Within the TB and HIV economic literature, there was a lack of standardized costs and utilities reported which made it very difficult to generalize findings between studies. We were not able to do meta-analysis for either literature review due to the underlying heterogeneity of the included studies. Studies did not always include programmatic costs in their economic evaluation, which led to an overestimation of costeffectiveness. Cost per case diagnosed was the most common outcome measured used, while cost per utility measure such as DALY averted or QALY was less common. Using at least one utility measure, would ensure that information about quality of life is included in economic evaluations. The lack of consistent outcomes from the systematic review, helped to inform our model. We made sure to include standardized costs and consistent outcome measures to allow our results to be generalized.

For both systematic screening for TB and HIVST, we found that the intervention was much more likely to be cost effective when implemented among groups with higher underlying prevalence of infection. From our model, we found that HIVST was cost effective when using a WTP threshold of 3 x GDP per capita. When a more conservative WTP threshold was used (of the GDP per capita), HIVST was typically cost effective when targeted towards high-risk subgroups. This suggests that a strategy that is cost effective among a particular subpopulation, is much less likely to be cost effective when applied to the general population. Screening programs that use additional resources to support linkage to confirmatory testing and follow up care, will be most cost effective when targeted to a specific high-risk group.

Implications for Future Research

Through our systematic reviews, we identified major gaps in the current literature that should be addressed moving forward. There was a lack of data around the cost effectiveness of systematic screening of TB in the pediatric population. Particularly among young children, symptomatic screening strategies like the WHO symptom screen (4SS) have much higher rates of false positives. Children represent approximately 10% of total infections globally and are important vectors of TB transmission[34] yet there have been no cost utility studies in children <15 years of age for systematic screening. Recently there have been some studies reporting efficacy and preference outcomes for HIVST among the adolescent population. There currently are no studies looking at cost effectiveness of HIVST among adolescents, butin the future, this should be investigated.

Summary

TB and HIV are infectious diseases that have been associated with significant stigma. Due to their underlying transmission pattern and risk factors, they disproportionately burden already marginalized populations who may face barriers to accessing conventional health care. From an advocacy perspective, health economics provides the methodology to evaluate the cost effectiveness of systematic screening and HIVST prior to investing health system resources. The economic model provides a tool that could help policy makers and health care professionals understand how to maximize the cost effectiveness of an HIVST program. The reality within the health care system is that resources are finite and optimizing cost effectiveness should translate into improved health outcomes.

Along with optimizing cost effectiveness, continued advocacy for increased funding and government level support for TB and HIV diagnosis and treatment programs will help advance the ambitious goal oferadicating TB and HIV related morbidity & mortality globally. Especially during the COVID-19 pandemic, where progress towards mitigating TB and HIV has stalled, it is imperative to continue to focus on early diagnosis and screening.

In summary, systematic screening and HIVST represent innovative methods of screening for infectious disease that have the potential to improve accessibility and uptake, particularly among marginalized communities. Our reviews and model suggest that they can be cost effective particularly when targeted tohigh-risk subgroups.

References:

1. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396: 1204-1222.
2. Leibler JH, Zakhour CM, Gadhoke P, Gaeta JM. Zoonotic and Vector-Borne Infections Among Urban Homeless and Marginalized People in the United States and Europe, 1990-2014. Vector Borne Zoonotic Dis. 2016;16: 435-444.
3. World Health O. Research priorities for zoonoses and marginalized infections. World Health Organ Tech Rep Ser. 2012: ix-xi, 1-119, 112 p following 119.
4. Springer YP, Kammerer JS, Silk BJ, Langer AJ. Tuberculosis in Indigenous Persons - United States, 2009-2019. J Racial Ethn Health Disparities. 2021.
5. UNAIDS. 2021. New HIV Infections. Retrieved July 11, 2021 from https://aidsinfo.unaids.org.
6. de Mendoza C. UNAIDS Update Global HIV Numbers. AIDS Rev. 2019;21: 170-171.
7. Harding E. WHO global progress report on tuberculosis elimination. Lancet Respir Med. 2020;8: 19.
8. Rathbun RC. HIV consensus guideline recommends antiretroviral treatment regardless of CD4 count, new regimens and possible regimen change for chronic low level viraemia. Evid Based Med. 2013;18: 149-150.
9. Lee-Rodriguez C, Wada PY, Hung YY, Skarbinski J. Association of Mortality and Years of Potential Life Lost With Active Tuberculosis in the United States. JAMA Netw Open. 2020;3: e2014481.
10. UNAIDS. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic. Retrieved September 8, 2021 from https://www.unaids.org/en/resources/documents/2017/90-90-902017.
11. Organization WH. End Tb Strategy: Global strategy and targets for tuberculosis prevention, care and control after 20152015.
12. Chen Q, Zeng D, She Y, et al. Different transmission routes and the risk of advanced HIV disease: A systematic review and network meta-analysis of observational studies. EClinicalMedicine. 2019;16: 121-128.
13. Cuadros DF, Awad SF, Abu-Raddad LJ. Mapping HIV clustering: a strategy for identifying populations at high risk of HIV infection in sub-Saharan Africa. Int J Health Geogr. 2013;12: 28.
14. Anderson P. Tuberculosis in Nunavut: a socioeconomic tragedy. CMAJ. 2011;183: 1053.
15. Altice FL, Azbel L, Stone J, et al. The perfect storm: incarceration and the high-risk environment perpetuating transmission of HIV, hepatitis C virus, and tuberculosis in Eastern Europe and Central Asia. Lancet. 2016;388: 1228-1248.
16. Feske ML, Teeter LD, Musser JM, Graviss EA. Giving TB wheels: Public transportation as a risk factor for tuberculosis transmission. Tuberculosis (Edinb). 2011;91 Suppl 1: S16-23.
17. Yang WT, Gounder CR, Akande T, et al. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? Tuberc Res Treat. 2014;2014: 461935.
18. Yin Y, Chen AC, Wan S, Chen H. Factors Associated With HIV-Related Stigma Toward People Living With HIV Among Nurses in Liangshan Yi Autonomous Prefecture, China: A Cross-Sectional Study. Front Psychiatry. 2021;12: 714597.

19. Zucker J, Carnevale C, Theodore D, et al. Attitudes and Perceived Barriers to Routine HIV Screening and Provision and Linkage of Postexposure Prophylaxis and Pre-Exposure Prophylaxis Among Graduate Medical Trainees. AIDS Patient Care STDS. 2021;35: 180-187.
20. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005;9: 1183-1203.
21. Eshun-Wilson I, Jamil MS, Witzel TC, et al. A Systematic Review and Network Meta-analyses to Assess the Effectiveness of Human Immunodeficiency Virus (HIV) Self-testing Distribution Strategies. Clin Infect Dis. 2021;73: e1018-e1028.
22. Cambiano V, Ford D, Mabugu T, et al. Assessment of the Potential Impact and Cost-effectiveness of Self-Testing for HIV in Low-Income Countries. J Infect Dis. 2015;212: 570-577.
23. Cambiano V, Johnson CC, Hatzold K, et al. The impact and cost-effectiveness of community-based HIV self-testing in sub-Saharan Africa: a health economic and modelling analysis. J Int AIDS Soc. 2019;22 Suppl 1: e25243.
24. Kelvin EA, George G, Mwai E, et al. Offering Self-administered Oral HIV Testing as a Choice to Truck Drivers in Kenya: Predictors of Uptake and Need for Guidance While Self-testing. AIDS Behav. 2018;22: 580-592.
25. Kelvin EA, George G, Mwai E, et al. Offering self-administered oral HIV testing to truck drivers in Kenya to increase testing: a randomized controlled trial. AIDS Care. 2018;30: 47-55.
26. Kelvin EA, George G, Mwai E, et al. A Randomized Controlled Trial to Increase HIV Testing Demand Among Female Sex Workers in Kenya Through Announcing the Availability of HIV Self-testing Via Text Message. AIDS Behav. 2019;23: 116-125.
27. Singh M, Sagili KD, Tripathy JP, et al. Are Treatment Outcomes of Patients with Tuberculosis Detected by Active Case Finding Different From Those Detected by Passive Case Finding? J Glob Infect Dis. 2020;12: 28-33.
28. Machekera SM, Wilkinson E, Hinderaker SG, et al. A comparison of the yield and relative cost of active tuberculosis case-finding algorithms in Zimbabwe. Public health action. 2019;9: 63-68.
29. Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet. 2010;376: 1244-1253.
30. Sekandi JN, Dobbin K, Oloya J, Okwera A, Whalen CC, Corso PS. Cost-effectiveness analysis of community active case finding and household contact investigation for tuberculosis case detection in urban Africa. PloS one. 2015;10: e0117009.
31. Shah L, Rojas M, Mori O, et al. Cost-effectiveness of active case-finding of household contacts of pulmonary tuberculosis patients in a low HIV, tuberculosis-endemic urban area of Lima, Peru. Epidemiology and infection. 2017;145: 1107-1117.
32. Hussain H, Mori AT, Khan AJ, et al. The cost-effectiveness of incentive-based active case finding for tuberculosis (TB) control in the private sector Karachi, Pakistan. BMC health services research. 2019;19: 690.
33. Mupere E, Schiltz NK, Mulogo E, Katamba A, Nabbuye-Sekandi J, Singer ME. Effectiveness of active case-finding strategies in tuberculosis control in Kampala, Uganda. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2013;17: 207-213.

34. Organization WH. Global tuberculosis report 2019 2019. Available from URL: Retrieved May 31, 2020 from https://www.who.int/tb/publications/global_report/en/.
35. Ma Y, Horsburgh CR, White LF, Jenkins HE. Quantifying TB transmission: a systematic review of reproduction number and serial interval estimates for tuberculosis. Epidemiol Infect. 2018;146: 1478-1494.
36. Rhee JT, Piatek AS, Small PM, et al. Molecular epidemiologic evaluation of transmissibility and virulence of Mycobacterium tuberculosis. J Clin Microbiol. 1999;37: 1764-1770.
37. Garcia-Garcia ML, Ponce de Leon A, Jimenez-Corona ME, et al. Clinical consequences and transmissibility of drug-resistant tuberculosis in southern Mexico. Arch Intern Med. 2000;160: 630-636.
38. Marquina-Castillo B, Garcia-Garcia L, Ponce-de-Leon A, et al. Virulence, immunopathology and transmissibility of selected strains of Mycobacterium tuberculosis in a murine model. Immunology. 2009;128: 123-133.
39. Kuupiel D, Bawontuo V, Mashamba-Thompson TP. Mapping evidence on tuberculosis active case finding policies, strategies, and interventions for tuberculosis key populations: a systematic scoping review protocol. Syst Rev. 2019;8: 162.
40. Shriraam V, Srihari R, Gayathri T, Murali L. Active case finding for Tuberculosis among migrant brick kiln workers in South India. Indian J Tuberc. 2020;67: 38-42.
41. Sawert H, Kongsin S, Payanandana V, Akarasewi P, Nunn PP, Raviglione MC. Costs and benefits of improving tuberculosis control: the case of Thailand. Soc Sci Med. 1997;44: 1805-1816.
42. Jit M, Stagg HR, Aldridge RW, et al. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ. 2011;343: d5376.
43. Van Hout MC, Stover H, Benamara K, Bauer P, Salah E. 90-90-90: catalysing the response to HIV by enhancing prison visibility in the Joint United Nations Programme on HIV and AIDS (UNAIDS) strategy beyond 2021. Public Health. 2021;190: e5-e6.
44. Parchem B, Molock SD. HIV testing preferences, barriers and facilitators to receiving HIV services among young Black sexual minority men. AIDS Care. 2021: 1-8.
45. Qin Y, Han L, Babbitt A, et al. Experiences using and organizing HIV self-testing. AIDS. 2018;32: 371-381.
46. Rivera AS, Hernandez R, Mag-Usara R, et al. Implementation outcomes of HIV self-testing in low- and middle- income countries: A scoping review. PLoS One. 2021;16: e0250434.
47. Indravudh PP, Fielding K, Kumwenda MK, et al. Effect of community-led delivery of HIV self-testing on HIV testing and antiretroviral therapy initiation in Malawi: A cluster-randomised trial. PLoS Med. 2021;18: e1003608.
48. Nguyen VTT, Phan HT, Kato M, et al. Community-led HIV testing services including HIV self-testing and assisted partner notification services in Vietnam: lessons from a pilot study in a concentrated epidemic setting. J Int AIDS Soc. 2019;22 Suppl 3: e25301.
49. Mangenah C, Mwenge L, Sande L, et al. Economic cost analysis of door-to-door community-based distribution of HIV self-test kits in Malawi, Zambia and Zimbabwe. J Int AIDS Soc. 2019;22 Suppl 1: e25255.
50. Pai N, Esmail A, Saha Chaudhuri P, et al. Impact of a personalised, digital, HIV self-testing app-based program on linkages and new infections in the township populations of South Africa. BMJ Glob Health. 2021;6.

51. George G, Chetty T, Strauss M, et al. Costing analysis of an SMS-based intervention to promote HIV self-testing amongst truckers and sex workers in Kenya. PLoS One. 2018;13: e0197305.
52. De Boni RB, Veloso VG, Fernandes NM, et al. An Internet-Based HIV Self-Testing Program to Increase HIV Testing Uptake Among Men Who Have Sex With Men in Brazil: Descriptive Cross-Sectional Analysis. J Med Internet Res. 2019;21: e14145.
53. Solberg CT, Norheim OF, Barra M. The disvalue of death in the global burden of disease. J Med Ethics. 2018;44: 192-198.
54. Solberg CT, Sorheim P, Muller KE, Gamlund E, Norheim OF, Barra M. The Devils in the DALY: Prevailing Evaluative Assumptions. Public Health Ethics. 2020;13: 259-274.

Appendix Table 1a

CHEERS Quality Assessment: Systematic screening for Tuberculosis

	Is the study population clearly described?	Are competing alternatives clearly described?	Is a well-defined research question posed in answerable form?	Is the economic study design appropriate to the stated objective?	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Is the actual perspective chosen appropriate?	Are all important and relevant costs for each alternative identified?	Are all costs measured appropriately in physical units?	Are costs valued appropriately?
Andre et. al	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
Azman et. al	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Bogdanova et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Daftary et. al	Yes	No	Yes	Yes	No	Yes	No	No	No
Eang et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hinderaker et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Htet et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hussain et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
James et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Jo et. al	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kranzer et. al	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lung et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Machekera et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Malik et. al	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
Mupere et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Murray et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Myint et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Nishikiori et. al	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sekandi et. al	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Shah et. al (Vietnam)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Yadav et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix Table 1b

CHEERS Quality Assessment: Systematic screening for Tuberculosis

	Are all important and relevant outcomes for each alternative identified?	Are all outcomes measured appropriately in physical units?	Are outcomes valued appropriately?	Is an incremental analysis of costs and outcomes of alternatives performed?	Are all future costs and outcomes discounted appropriately?	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Do the conclusions follow from the data reported?	Does the study discuss the generalizability of the results to other settings and patient/client groups?	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?
Andre et.	No	No	No	Yes	No	No	Yes	Yes	Yes

al									
Azman et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bassett et. al	No	No	No	Yes	No	No	Yes	Yes	Yes
Bogdanova et. al	Yes	Yes	No	Yes	No	No	Yes	No	Yes
Daftary et. al	Yes	Yes	No	Yes	No	No	Yes	No	Yes
Eang et. al	Yes	Yes	No	Yes	No	No	Yes	No	Yes
Hinderaker et.al	Yes	Yes	No	Yes	No	No	Yes	Yes	No
Htet et. al	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes
Hussain et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
James et. al	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Jo et. al	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Lung et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kranzer et. al	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Macheker a et. al	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Malik et. al	Yes	Yes	No	Yes	No	No	Yes	No	Yes
Mupere et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Myint et. al	Yes	Yes	No	Yes	No	No	Yes	No	Yes
Nishikiori	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

et. al									
Sekandi et. al	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Shah et. al (Peru)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Yadav et. al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No