INTERVENTIONS TO IMPROVE HEALTH SERVICES AND PREVENT TUBERCULOSIS FOR PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS IN SOUTH AFRICA

by

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ABSTRACT

Background: South Africa is home to nearly seven million people living with human immunodeficiency virus (PLHIV), for whom tuberculosis (TB) is the leading cause of death. Although national guidelines include effective tactics to prevent TB for PLHIV, implementation has been suboptimal.

Objectives: The goal of this dissertation was to evaluate interventions to improve TB prevention for PLHIV in South Africa. We delivered patients' lab results via mobile phone to more quickly recall people with TB or other medically concerning results (Chapter 2). We then sought to improve prescriptions of TB preventive therapy (TPT) with an alternative diagnostic for latent TB infection (LTBI, Chapter 3) and with education campaigns and nurse mentorship (Chapter 4).

Methods: For Aim 1, we implemented a non-randomized pilot to compare delivering test results via MatlaMobile versus the standard-of-care. For Aim 2, we conducted a cluster randomized trial to evaluate whether a Quantiferon Gold In-Tube (QGIT) test resulted in more LTBI results being documented and TPT prescriptions than standard-of-care. For Aim 3, we directly observed an intervention and conducted qualitative interviews to characterize implementation outcomes.

Results: In Aim 1, patients who received their results via phone were more likely to return to the clinic within seven days, if instructed that their result was medically concerning (20%, n=14/70) than the control group, who were all instructed to return to the clinic to retrieve their results (9%, n=15/174, p=0.02). In Aim 2, clinics documented an absolute 60% (95% CI: 51–68; p <0.001) more LTBI results and 12% (95% CI: –6, 31, p = 0.179) more TPT in QGIT clinics than the standard-of-care, after adjusting for baseline covariates. In Aim 3, the intervention was implemented with moderate fidelity and high uptake, however, nurses questioned whether the intervention could sustain its impact without structural changes.

Conclusions: These interventions improved retention-in-care and TB prevention for PLHIV. However, none persuaded patients and nurses to fully adhere to recommended TB/HIV guidelines. Future work should incorporate structural-level interventions, like increased staffing and improved TPT stock management, to better prevent TB among PLHIV.

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CHAPTER 1: INTRODUCTION

Overview

Tuberculosis (TB) is a major driver of mortality worldwide and is particularly dangerous for people with human immunodeficiency virus (HIV). To reduce TB morbidity and mortality among people living with HIV (PLHIV), extensive efforts have been made to craft policies that encourage simple, targeted, and cost-effective TB prevention, diagnosis, and treatment. However, implementation of such policies remains suboptimal in many resource-scarce regions where it is challenging to deliver quality healthcare and to retain patients. This dissertation applies existing research about barriers to TB/HIV care to design and evaluate three interventions to improve the delivery of TB diagnoses and uptake of TB preventive therapy (TPT) for PLHIV in the Northwest Province of South Africa.

First, I sought to reduce unnecessary clinic visits and improve engagement-in-care by sending HIV viral load (VL), CD4 counts, and TB test results via mobile phone (Aim 1, Chapter 2). Second, I aimed to increase the number of PLHIV who received a TB immunoreactivity test and a prescription for TPT (Aim 2, Chapter 3). Finally, I explored the motivations and misgivings of nurses and PLHIV in clinics where TPT prescriptions increased after an education-based intervention (Aim 3, Chapter 4). In this chapter (Chapter 1), I provide an overview of the epidemiology of TB among PLHIV; the natural history of TB infection; methods and barriers of TB prevention; and the specific context of the cities of Klerksdorp and Potchefstroom where this research was located.

Epidemiology of Tuberculosis among PLHIV

Among the 38 million PLHIV globally in 2019, there were 815,000 new cases of TB disease [1,2]. These incident TB cases among PLHIV represented 8.2% of all cases [1]. Despite a nearly 70% reduction in TB deaths among PLHIV over the past two decades, TB remains the leading cause of death for PLHIV [1,2]. The TB/HIV syndemic is centered in sub-Saharan Africa, which is home to five of every eight new cases of HIV-related TB and 80% of the 214,000 HIV-related TB deaths each year [1,3,4]. The interplay and resulting incidence of TB and HIV are driven by interconnected risk factors at multiple socioecological levels (Figure 1.1).

PLHIV have a 20-fold higher risk of TB disease after exposure, as compared to people without HIV, with higher HIV viral loads being positively correlated to the risk of TB [5]. HIV compromises the immune system, rendering it less capable of clearing or containing TB infection [6–8]. Antiretroviral therapy (ART) can improve immune function for PLHIV and therefore lessen the risk of TB, however, this risk is still elevated as compared to people without HIV [9,10]. Many individual-level risk factors for TB — smoking [11,12], undernutrition [12,13], diabetes [11,14], and alcohol use [11,12]— work by weakening the immune system, among other mechanisms, and are commonly found among PLHIV [15–19]. Certain risk factors, such as alcohol use, are also associated with or may even reduce ART adherence and further impair immune function [20].

The risk of TB among PLHIV is also exacerbated by a myriad of socioeconomic and structural factors. TB has historically been associated with poverty, one of many key social determinants of health [21,22]. Poverty, in addition to contributing to under- and malnutrition, also subjects people to frequent TB exposure through living, traveling, and working situations that are overcrowded and poorly ventilated [23,24]. For example, certain occupations, such as healthcare providers and miners, may have extensive exposure to TB from working in generally enclosed spaces in close contact with others and, in the case of miners, extensive exposure to silica, a lung carcinogen [25,26]. Poverty also prevents people with TB from accessing quality healthcare, which can lead to delayed diagnoses and treatment; both of which contribute to onward transmission [27]. Ending extreme poverty at a global scale would have a substantial impact on TB, cutting incidence by a third [28]. However, TB incidence could be even further diminished, reduced by 84%, with the provision of comprehensive sociostructural protections like food rations, free healthcare, social insurance, and unemployment benefits [28]. Structural-level factors, like economic recession and subsequent austerity measures that reduce government spending on public health services, are also key drivers of TB disease worldwide [29].

Basis of Tuberculosis Control among People without and with HIV

Natural history of tuberculosis

Humans are the primary reservoir of the rod-shaped, acid-fast Mycobacterium tuberculosis that causes TB disease [30,31]. The natural history of TB (Figure 1.2) begins with exposure to droplet nuclei containing M. tuberculosis expelled from an infectious person through coughing, sneezing, singing, or other expiratory activities [31,32]. After exposure, an individual may clear the bacteria, some of whom will remain immunoreactive; others will develop a latent TB infection (LTBI) [33]. In a minority of immunocompetent people, initial immune containment will fail and LTBI will progress to active TB, with an approximate 5-10% lifetime risk of progressing, also known as "reactivation" [34]. For people who progress to active TB, the incubation period from exposure to TB symptoms is typically several months to two years, and 80% of cases will develop into pulmonary TB, i.e., of the lungs or respiratory system [35].

Although the binary of "latent" and "active" TB has persisted as dogma, new studies suggest that TB exists along a more nuanced spectrum — including minimal, incipient, subclinical, and lastly, active disease [33,36,37]. Minimal disease includes slight *M. tuberculosis* metabolic activity; incipient disease indicates imminent advancement to a subclinical disease [33,37]. While minimal and incipient disease are neither bacteriologically nor radiographically detectable, subclinical disease can be detected, yet it does not cause the individual to manifest with TB symptoms such as cough, weight loss, fever, and night sweats,

as active disease does [37]. However, both subclinical and active disease are contagious [33]. Distinguishing between these stages is crucial for the prevention and control of TB.

Unfortunately, differential tools are either non-existent or often scarce in places where they are needed most. For example, we cannot differentiate between a person who has cleared a TB infection but who remains immunoreactive and a person with LTBI [33]. As such, treatment-naïve people who are TB immunoreactive are presumed to have LTBI. To differentiate between subclinical and active disease, an x-ray or bacteriological test might be of service, but are lacking in resource-constrained areas. For regions with a high TB burden, critical gains could be made through universal screening to catch subclinical disease, which makes up 36-80% of bacteriologically confirmable TB [37,38].

For PLHIV and other immunocompromised groups, TB disease is often more complicated and insidious. As stated before, PLHIV are more likely to progress to active TB [5]. Additionally, PLHIV are more likely to develop TB outside of the lungs, a type known as extrapulmonary TB (ETB) [39]. ETB often manifests with fewer bacilli (i.e., paucibacillary), presents atypically, and is more difficult to diagnose clinically or bacteriologically [40]. In the advanced stages of HIV, individuals also frequently lack an immunological response to the presence of *M. tuberculosis* and have fewer or no TB symptoms [41–43]. As such, they may appear as if they have never been exposed to TB [44,45]. When a person

with low immune function begins ART, which can restore TB-specific immunocompetence, they may “unmask” their TB disease because the revived immune response will result in new symptoms such as fever and coughing [46]. In extreme but rare cases, the immune response can go into overdrive and result in necrotic, sometimes fatal, inflammation [46].

Although we have so far focused on the impact of HIV on the course of TB, some research suggests that TB can affect the course of HIV as well. People with LTBI may be at an increased risk of HIV infection, allow HIV to more easily evade the immune system, and cause a higher initial viral load after primary HIV infection, which can increase onward transmission of HIV and accelerate HIV disease progression [47].

Prevention of tuberculosis

Interventions to prevent and control TB exist for nearly every step along its natural history [32,48,49]. To prevent infection, the live attenuated Bacillus Calmette-Guérin (BCG) vaccine is part of many childhood immunization schedules in countries with a high TB burden [50]. The effectiveness of the vaccine against pulmonary TB varies extensively from study-to-study and across populations, though one systematic review pins its effectiveness around 60% for people vaccinated as neonates [50]. Infection can also be prevented by finding, isolating, and treating people with subclinical or active TB disease through passive, active, or community-based case finding [51]. Within clinics that

diagnose and treat TB patients, healthcare providers can take a myriad of precautions to reduce TB transmission from potential cases, including masking, proper ventilation, separate wait areas, asking people suspected tof TB to take their respiratory samples out-of-doors, and minimizing queues to decrease the time that patients spend at the clinic [52]. Other intervention strategies, which are considered key components for reaching international goals for TB control, include retaining patients in care and the provision of TPT to people with LTBI who are at high risk of progressing to active disease [53,54]. The process for prescribing TPT involves multiple steps and is also known as the LTBI cascade of care [55].

The cascade of care for latent tuberculosis infection

Though the order and specifics of the LTBI care cascade vary from region to region, the steps generally remain consistent. In the first step, healthcare providers identify people at high risk of TB disease. According to the World Health Organization (WHO), this includes all PLHIV of any age, household contacts of TB cases, patients receiving dialysis, patients preparing for organ transplants, and people with silicosis [56]. In areas where TB is uncommon, systematic LTBI screening may also be conducted in key populations such as immigrants from regions with a high prevalence of TB, prisoners, and healthcare providers [56]. Though tobacco, diabetes, and alcohol also contribute to TB

vulnerability, the WHO does not recommend regular screening for people with these risk factors [56].

In the second step, patients are tested for TB immunoreactivity, which is assumed to indicate a LTBI, via a tuberculin skin test (TST) or an interferon gamma release assay (IGRA). To conduct a TST, a trained healthcare provider intradermally injects tuberculin purified protein derivative (PPD) into a patient's forearm and then recalls the patient within 48-72 hours for interpretation [57]. For people who have previously been exposed to and developed a cell-mediated immune response to TB (i.e, "immunoreactive"), the body's lymphocytes react to the PPD by releasing cytokines, including interferon gamma (IFN-γ), to create an induration and redness at the site of injection. A healthcare provider then measures the diameter of the induration and interprets its size against standard cutoffs that vary according to the patient's susceptibility [58]. IGRAs leverage the same underlying immunological principal but are conducted in vitro with a whole blood sample; two commercially available tests were popular at the time of this dissertation between 2014-2019: Quantiferon Gold In-Tube (QGIT) and the T.SPOT.TB [59,60]. Many low- and middle-income countries do not require LTBI testing for PLHIV prior to TPT initiation [61].

In the third step, healthcare providers interpret the LTBI test results and complete a medical examination to exclude the possibility of active TB. Depending on the setting, the exam may consist of a symptom screening, physical checkup, and/or chest radiography [52]. This step is critical, as the same

drugs are used to treat LTBI and active TB; though the first-line treatment for active TB employs a four-drug combination therapy while LTBI typically employs a monotherapy or two-drug combination [56,62]. Providing LTBI treatment to a patient with active TB, or non-adherence, may result in drug-resistant TB [63].

In the fourth step, healthcare providers prescribe TPT to patients who were TB immunoreactive (i.e., presumed to have LTBI) but had no evidence of active TB. In high-burden TB regions, the 2020 WHO Consolidated Guidelines for Tuberculosis also recommend up to 36 months of TPT for PLHIV who do not know their LTBI status [56]. TPT comes in many forms, though the first was isoniazid monotherapy (INH), which was tested in 1961; the six to nine month regimen remains a cornerstone for treating LTBI today [64–67]. Since then, shorter combination therapies have emerged, including three months of daily INH with rifampin (3HR) and three months of weekly INH with rifapentine (3HP) [68,69]. Common side effects of TPT include upset stomach, painful or swollen joints, dizziness, fatigue, seizures, peripheral neuropathy, impaired liver function, and rarely, neutropenia [70,71]. In the final step, patients adhere to and complete their recommended regimen. Of adult patients on INH, approximately 7% have adverse events due to the drug, with that proportion being higher for shorter regiments (12% for 3-6HR; 28% for 3HP) [72].

Scale up and barriers to tuberculosis preventive therapy for PLHIV

In 2008, the WHO launched the "Three I's" initiative as a strategy to reduce TB among PLHIV: (1) Intensified case finding, (2) **I**NH and other TPT, and (3) **I**nfection control [53]. Building on this framework, the WHO set the goal of 90% eligible PLHIV be started on TPT by 2025 [73]. TPT quickly increased worldwide, with the greatest gains being made in southern Africa [74]. Implementation in resource-scarce regions, however, has slowed and since plateaued to 33–42% of PLHIV completing their TPT regimens worldwide [61]. The LTBI cascade of care offers a useful framework to categorize reasons for attrition and to explain the suboptimal levels of TPT for PLHIV.

First, due to lack of time, lack of training, or both, healthcare providers do not consistently identify PLHIV as eligible for TPT [61]. Second, for PLHIV identified as eligible, not all are screened for active TB. This may be because resource-scarce regions can rarely afford to bacteriologically or radiographically rule out active TB for every patient. However, the WHO recommends a screening tool for all PLHIV based on four common TB symptoms (WHO4SS); the tool is 82% sensitive and 42% specific among ambulatory PLHIV in low- and middle-income countries [75]. Though the WHO4SS has generally high uptake, recent studies demonstrate that the WHO4SS misses a substantial proportion of PLHIV with ETB or subclinical disease and is considered insufficient for ruling out TB disease by some healthcare providers, especially in an era of ART [38,76–78].

Third, TST remains the primary LTBI test for regions that cannot afford IGRAs. However, in addition global shortages of TST supplies, the test has many other drawbacks. TSTs require healthcare providers to be specially trained in placing and reading the test, while also depending on patients to return within a specified timeframe. Furthermore, TST is cross-reactive to non-tuberculosis mycobacterium as well as the bacille Calmette-Guerin (BCG) vaccine, which is routinely given to infants in resource-scarce regions. The IGRA, while more expensive, can distinguish between LTBI and BCG. Both, however, measure immune response, and their performance is often less sensitive among PLHIV [79,80]. A negative LTBI test may mean that there are no viable *M. tuberculosis* or that the body's T cells are anergic (i.e., incapable of responding) due to the HIV infection.

Fourth, in resource-scarce regions, the largest loss from the LTBI cascade of care tends to occur when healthcare providers are supposed to prescribe TPT [61]. In low-income countries that did not require an LTBI test, 34% of eligible PLHIV were not prescribed TPT. The commonly cited reasons for failure to prescribe include lack of training, fear of encouraging drug-resistant TB, difficulty and burden of counseling PLHIV, mistrust of PLHIV who are already non-adherent to ART regimens, lack of baseline liver function tests to monitor patients for side effects, and concerns about stock outs that might interrupt adherence [61]. Prescriptions of TPT are also complicated by potential drug-drug

interactions with ART, lack of guidance regarding how to time initiation relative to ART, and the separation of TB/HIV care [81,82].

Lastly, patients may not initiate or adhere to TPT due to lacking information or counseling about the treatment, being over-burdened with pills, fearing or experiencing side effects, not wanting to give up drinking alcohol, not returning to clinic to refill their prescription, and other reasons commonly cited for non-adherence to other drugs such as ART [83,84].

Despite the effectiveness of TPT and the plethora of research on increasing adherence with shorter regimens, a majority of PLHIV are already lost from the LTBI cascade-of-care before ever receiving a prescription [61]. Several health service delivery gaps, especially in low- and middle-income regions, are stalling global progress toward the End TB Goal of 90% of eligible PLHIV receiving TPT [84,85]. This research aimed to evaluate three health service interventions to improve TB prevention and diagnoses in the context of a resource-constrained area of South Africa, a country with a TB/HIV syndemic.

Study Location and Context

South Africa was home to more than 59.6 million people in 2020 [86]. Overall HIV prevalence was 13.0%, and among people aged 25-49 years, prevalence was 18.7% [86]. There were 328,000 new cases of TB, with 71% of those cases being among PLHIV and 2% being either multi-drug resistant (MDR)

or extensively drug resistant (XDR) [87]. These statistics place South Africa on the WHO's list of high burden countries for TB, TB/HIV, and MDR/XDR TB [3].

Overview of Klerksdorp and Potchefstroom, South Africa

This research was conducted between the years 2015 – 2018 in the cities of Klerksdorp and Potchefstroom, as well as several nearby townships, which are located in the Dr. Kenneth Kaunda district in the Northwest Province of South Africa (Figure 1.3). The Dr. Kenneth Kaunda district is home to 742,000 people. The HIV prevalence and TB incidence in the district were somewhat greater than the national average, at 13% and 696 per 100,000 respectively [88,89]. Unemployment in the district among people aged 15-34 years was at 39% [90]. Dr. Kenneth Kaunda district was primarily Black (81.7%), and all study clinics served areas that were also majority Black [91]. Klerksdorp and Potchefstroom are both located north of the Vaal River along the N12 Treasure Route Highway, which wends across the Witwatersrand Basin, home to the world's largest known gold reserves [92].

Through the sixteenth century, this region was solely inhabited by a mixture of Sotho and Tswana people, who both culturally and physically resembled nearby Bantu-speaking people across central, southeast, and southern Africa [93]. White settlers slowly encroached on the region between 1652, when the Dutch established a colony in modern day Cape Town, and 1820, when the British wrested control of the Cape Colony and began to expel

the Dutch [94]. However, in the late 1830s, nearly 10% of the white population in Cape Town, known as “Boers,” marched eastward during a massive migration event, “The Great Trek” [94]. Klerksdorp and Potchefstroom were the first and second white settlements of the Boer Republic [95,96]. Klerksdorp later became one of many gold mining towns on the Witwatersrand Basin, with several active operations to this day [95]. Potchefstroom, in contrast, was the original capital of the South African Republic established by the Boer and British in 1852; however, the capital was moved to Pretoria during the Boer Wars [96]. Today, Potchefstroom is home to several chemical engineering and poultry industries as well as being a major collegiate hub with the North-West University, the country’s second largest [96,97].

Historical setting of tuberculosis and healthcare in South Africa

Although western-trained physicians claimed that South Africa was seeded with TB by white settlers in the 1650s, “if a Zulu is asked the question [where did TB come from?], he answers, ‘it has always been with us’” [98]. Indeed, TB may not have been widely recognized by colonial healthcare providers, but this is likely due to limited diagnostic tools, a lack of care seeking from Black South Africans, and completely passive case finding [98]. TB began rapidly “appearing” in Black South Africans at the turn of the nineteenth century, alongside forced changes in lifestyle— from scattered populations who hunted, gathered, herded, and farmed in relatively small and well-fed units to

overworked, impoverished, and malnourished people living in densely compacted urban areas [99]. Although hospitals were installed in most major cities by the mid-1800s, the system was entirely segregated, with missionaries providing a majority of western-style healthcare to Black South Africans [100]. Further fragmentation of public healthcare services occurred around 1887, at which time curative and preventive care were separated, and again in 1919 when preventive care became the responsibility of local governments instead of provinces [100].

Operating separately from these public health services, gold mines offered their own private healthcare to employees while simultaneously playing a crucial role in the production and dissemination of TB [101]. As Black South Africans were dispossessed of their farming lands and herds by white settlers and faced proletarianization, many were forced to seek wages from nearby gold mines beginning in 1885 [102]. At first, recruitment to the mines was difficult because pay was low and the work was strenuous [103]. Many people with TB, including those immigrating from Europe, were employed despite their ill health [103]. Eventually mining became a cornerstone of the Transvaal, with mines employing 10,000 laborers in 1889; 200,000 in 1910; and 400,000 in 1940 [100]. The demanding conditions of mining wore on workers and often caused LTBI to progress to active TB [103]. While working underground, sick miners easily infected healthy counterparts because they labored shoulder-to-shoulder in narrow and poorly ventilated spaces alongside axial, water-fed drills, which reduced silica dust but created humid conditions that encouraged TB

transmission [103]. Furthermore, housing aboveground was crowded and pay was insufficient to purchase nutritional meals [103]. Mining companies, though they increasingly provided improved healthcare to its employees, were economically disincentivized from detecting TB early [104]. Miners would often be allowed to progress to a deadly stage of the disease because workers compensation did not need to be paid to a miner who had already died [104]. If a miner became too ill to continue working or they reached the end of their six- to nine-month shift, they returned to their homes, often in rural outlying villages, along with their newly activated and infectious TB [105]. This pattern strongly contributed to establishing TB as essentially endemic to South Africa.

Although the early 1940s saw the creation of community health centers for Black South Africans, the Nationalist party took political control in 1948 and legislated violently to perpetuate and solidify decades of segregation into apartheid [100,106]. Color-specific housing was created outside urban areas through the “Urban Areas and Slum Clearance Acts” while the “Illegal Squatters Act” of 1951 allowed the state to “endorse out” (i.e., forcibly remove) Black South Africans from living in white areas or non-designated squatter camps [106]. Housing in color-specific areas was frequently overcrowded and unsanitary, and exploitive labor practices essentially guaranteed malnourishment despite token food programs [106]. Healthcare services were systematically underfunded or non-existent for Black South Africans, for whom nonprofit missionary hospitals continued to be the primary option, while white South Africans were treated to

“some the highest standards of health care in the world” [100,107]. Care was also further fragmented with the establishment of individual health departments for each “Black homeland” decreed by apartheid rule [100]. Although TB numbers reportedly declined under the Nationalists, this is likely an illusion caused by a combination of underreporting and the removal of Black South Africans beyond the “statistical boundaries of ‘white’ South Africa” [106,107].

These conditions positioned South Africa for a major upsurge of TB by the early 1980s. As domestic resistance to apartheid strengthened and ultimately succeeded in overthrowing the draconian social and physical barriers in the late 1980s and early 1990s, a new antagonist was emerging— HIV [108]. Despite the burgeoning HIV epidemic, there was little action or acknowledgment of it from Nelson Mandela, who was democratically elected president in 1994 and faced a host of pressing issues including reconciliation, political stability, economic reform, and international relations [109]. Although he would later become an avid advocate for tackling the HIV epidemic, the 1990s were an era of unchecked, exponential HIV transmission [100]. In all likelihood, the spread of HIV was heightened by the pre-existing, widespread presence of LTBI, especially among Black South Africans who had been oppressed and subjected to impoverished conditions with poor access to medical care [22,47].

In 2000, Thabo Mbeki was elected president; at this point, one in eight South African adults were living with HIV [110,111]. Although Mbeki endorsed anti-poverty programs to promote good health, his focus was singular and

excluded evidence-based science on HIV transmission and the lifesaving ability of ART [110]. Furthermore, Mbeki promoted conspiracies that ART was a plot to kill Africans and initially blocked ART distribution from public clinics [110]. He also appointed Manto Shabalala-Msimang as minister of health, who endorsed specific foods to prevent HIV and would later block the United States from funding ART [110,112]. With large swathes of the population left immunosuppressed, the HIV epidemic caused a massive resurgence of TB [47]. By 2008, South Africa accounted for 1% of the global population but 24% of all new HIV-related TB cases [5,34].

In 2009, with the election of Jacob Zuma, the South African ART program began to take an unexpected turn. Although Zuma had infamously claimed that showering reduced one's risk of HIV, he later ramped up what would become the world's largest ART program, with nearly two million people on ART by the end of 2012 [110]. This mass distribution of ART began to reduce the incidence and mortality of HIV-related TB [113–115]. To combat the TB epidemic, the South African Department of Health (DOH) issued a 2010 policy that all PLHIV without active TB disease should receive TPT to treat LTBI [116]. Then, in 2015, the Department of Health updated their TPT policies to be more stringent; the policy stated that all PLHIV should receive an LTBI test, specifically a TST, prior to or within one month of, prescribing TPT [117]. Although the post-apartheid health system saw the construction of more than 1,300 clinics across South Africa and policies that enacted free primary healthcare for all, this vision of improved care

for Black South Africans was and continues to be restricted by a chronic shortage of doctors and nurses due to the exclusion of Black Africans from many medical schools, a lack of trained leadership, and large gaps between policy and implementation [100].

This setting — widespread availability of ART for PLHIV with advanced disease, a newly contradictory TPT policy for PLHIV, and a deficit of healthcare workers — is the historical context in which the three studies from this dissertation were conducted.

Improving Health Service Delivery for PLHIV

To address these challenges, we undertook three interventions to improve health service delivery to reduce unnecessary in-person visits for PLHIV, retain high-risk patients in care, and provide TPT to eligible PLHIV (Figure 1.4). To conclude this chapter, I summarize the state of the literature for each of the upcoming aims.

First, TB/HIV patients often have difficulty accessing care, report poor overall service experiences, and are required to return unnecessarily [84,118,119]. Despite free-of-charge ART, TB treatment, and TPT, patients often cannot afford time away from work or the cost of travel; for some, missing a day from their job may endanger their employment altogether [119,120]. Patients in South Africa also wait for hours at public clinics before receiving care, or are even turned away if queues become too long, which discourages them from

returning [118,119,121,122]. For PLHIV, the only way to receive routine test results is to return in-person, but many results do not require further action, such as an undetectable viral load or negative bacteriological TB screen. The clinic can be especially dangerous for PLHIV because it includes an elevated risk of being exposed to TB [34]. There is an urgent need for PLHIV to avoid unnecessary visits to the clinic while continuing to receive routine test results. Prior research in South Africa indicates that text message interventions may improve adherence to ART and TB treatment, though there are some concerns about privacy [123–125]. In Aim 1, I investigated whether mHealth can securely deliver HIV VL, CD4, and TB results to patients to reduce unnecessary visits to the clinic and to better retain high-risk patients in care.

Second, The rollout of TPT for PLHIV in South Africa was marred by numerous challenges [84]. PLHIV were unfamiliar with TPT, misunderstood its role as preventive therapy when feeling well, and were hesitant to add additional pills to their already heavy regimen [83,118–120,126,127]. Healthcare providers were not well educated about TPT and opted not to use it for fear of antibiotic resistance [77,128]. Furthermore, after new TPT policies were announced, the details for implementation remained unavailable in print for clinics to use as a reference [129]. South African nurses appear highly accepting of interventions that provide education about the evolving TPT guidelines and training to place and read TSTs, yet such interventions have only yielded small, short-term changes [76,130]. We currently lack a thorough understanding of why intense

educational and mentorship efforts were unsuccessful. In Aim 2, I assessed the fidelity, adoption, acceptability, and sustainability of a highly-tailored, clinic-specific educational interventions among nurses and PLHIV.

Lastly, healthcare providers have cited the newly added requirement for TST and complicated clinical algorithms as substantial barriers to TPT for PLHIV [76,131,132]. New technologies, such as IGRAs, have increased patient retention in the LTBI cascade in studies conducted in the United States [133]. Despite a plethora of education-based, individual-level interventions to promote TPT among South African nurses, there has been a deficit of structural-level interventions [76,130,131,134]. For Aim 3, I evaluated whether integrating IGRA testing into standard HIV care would increase the number of patients with documented LTBI test results and TPT prescriptions.

Figure 1.1 – Socioecological model of risk factors for TB/HIV

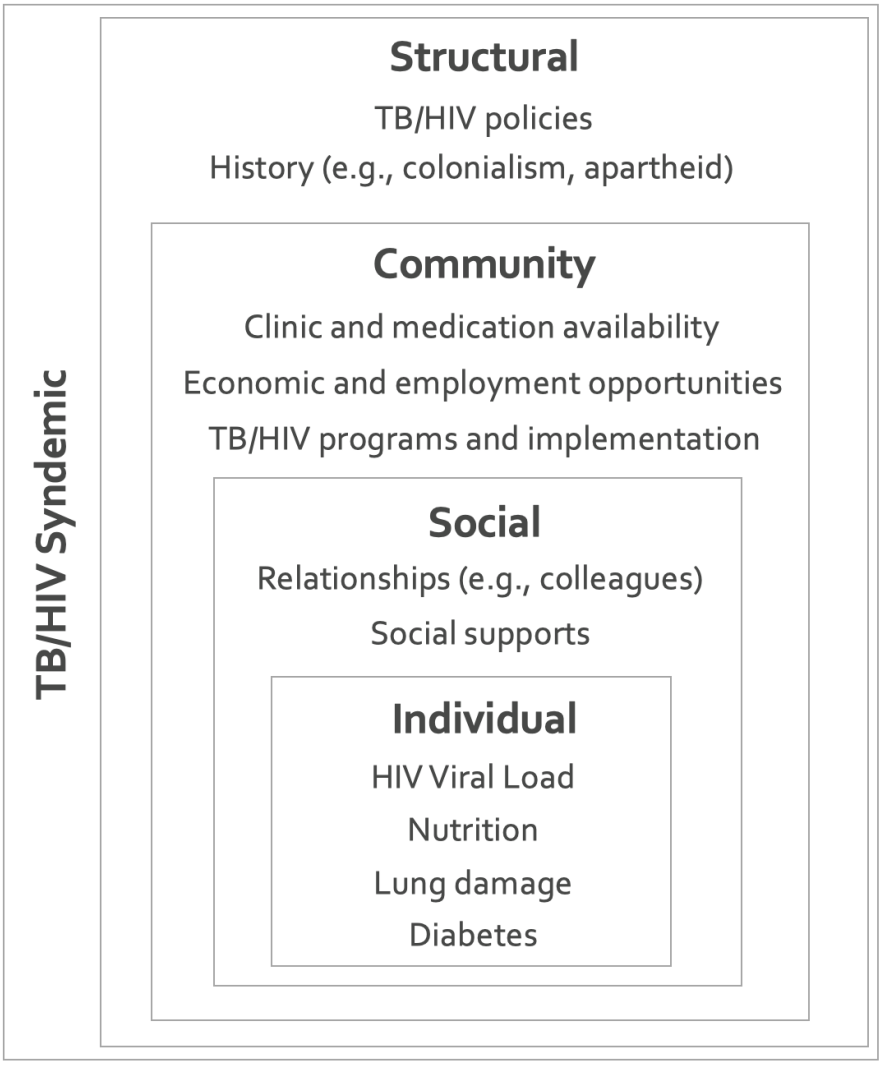


Figure 1.2 – Simplified natural history of tuberculosis

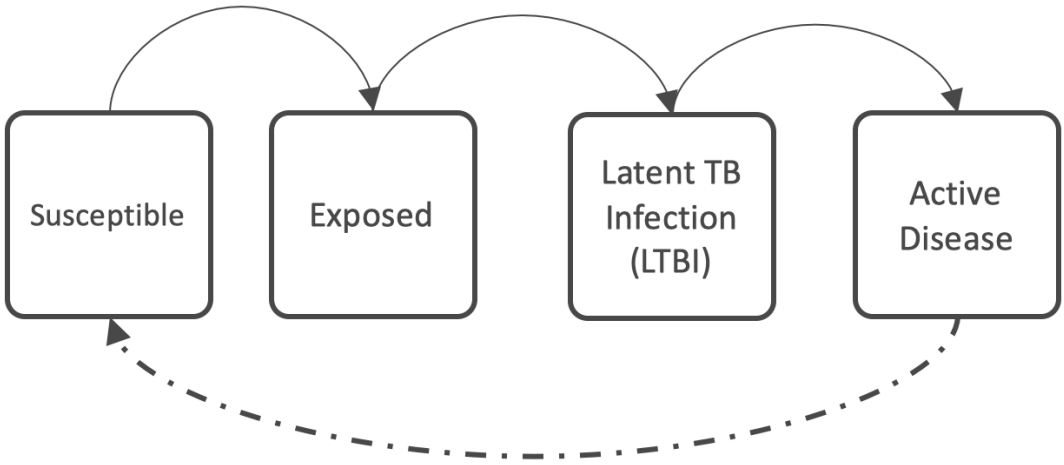


Figure 1.3 – Map of Klerksdorp and Potchefstroom on the Witwatersrand Basin in the Northwest Province of South Africa. Image from Nhlengetwa [135].

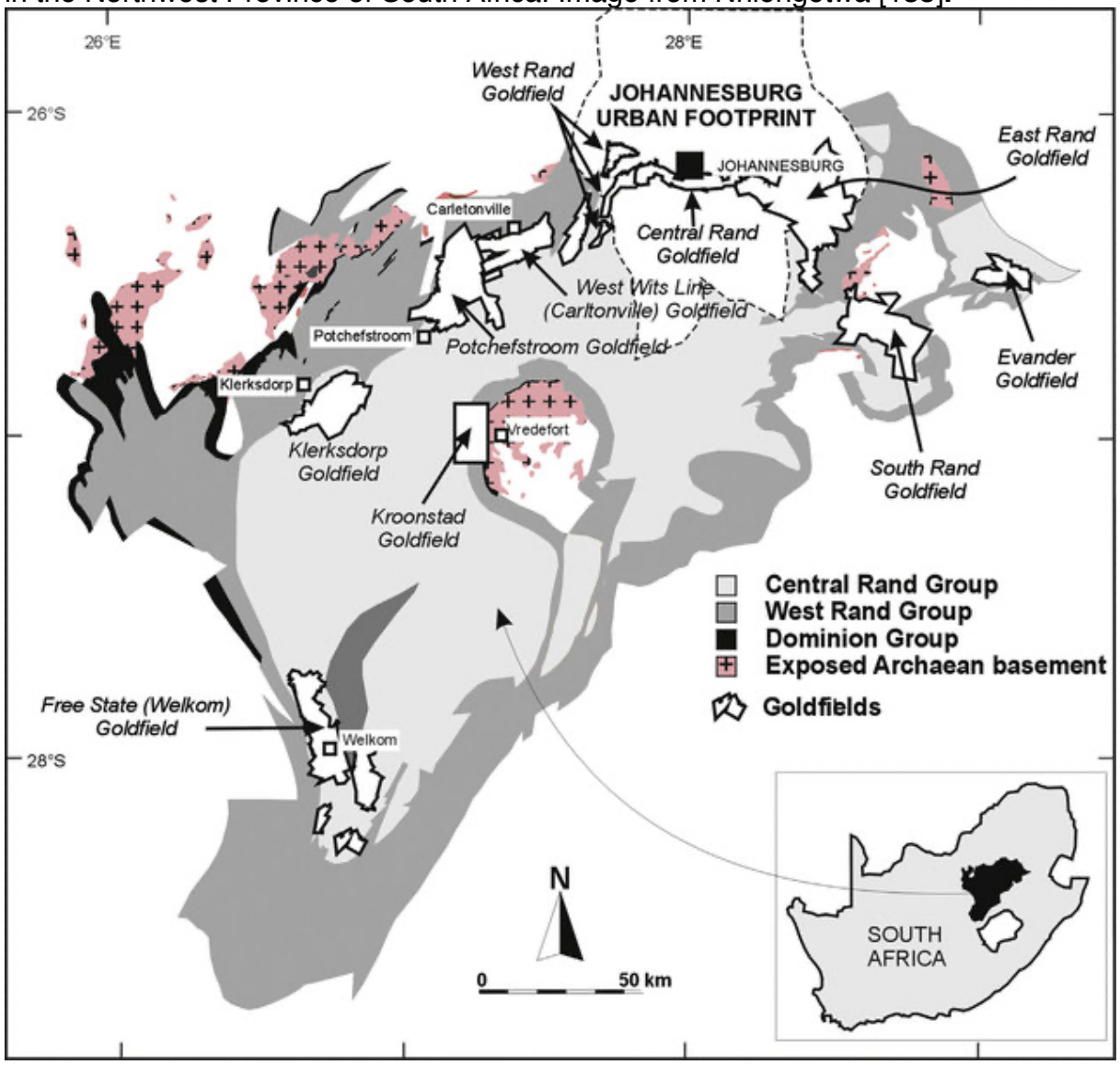
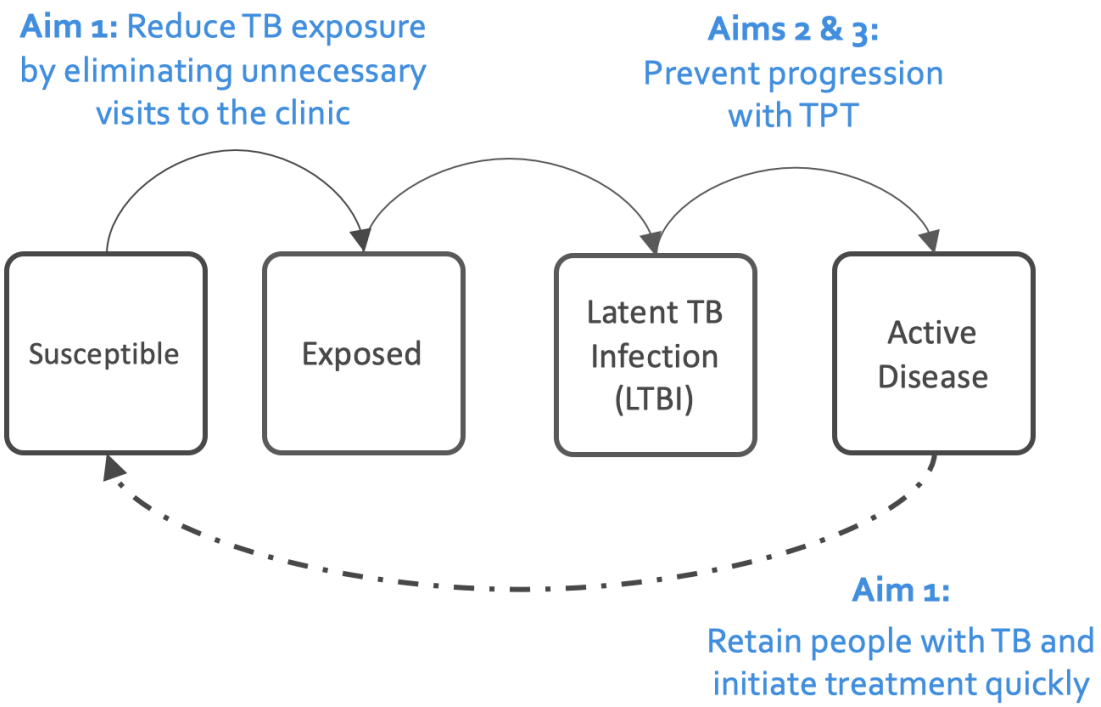


Figure 1.4 – Proposed aims to intervene on the natural history of tuberculosis



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CHAPTER 2: SECURE DELIVERY OF HIV-RELATED AND TUBERCULOSIS LABORATORY RESULTS TO PATIENT CELL PHONES: A PILOT COMPARATIVE STUDY

Abstract

South Africa processed 5.1 million HIV CD4, viral load (VL), and tuberculosis (TB) tests annually in 2016. This pilot non-randomized trial in South Africa explored an intervention ("MatlaMobile") to deliver laboratory results via mobile phone. Adults completing CD4, VL, and/or TB laboratory tests were enrolled — either receiving results by returning to clinic (control, n=174) or mobile phone (intervention, n=226). Study staff instructed control participants to return within six days (standard-of-care). MatlaMobile instructed intervention participants with clinically actionable results requiring intervention or treatment change (i.e., <200 CD4 cells per milliliter, ≥400 viral copies per milliliter, or TB positive) to return immediately. A greater proportion of intervention participants than controls saw their results within seven days of enrollment (73% vs. 8.6%, $p<0.001$). Among participants instructed to return, more intervention participants (20%, n=14/70) returned than controls (8.6%, n=15/174, $p=0.02$). MatlaMobile demonstrated that patients can quickly receive and respond appropriately to digital delivery of health information.

Introduction

The South African healthcare system is under-resourced to care for its 7.2 million patients living with human immunodeficiency virus (HIV) and 322,000 new cases of tuberculosis (TB) diagnosed in 2019 [1,2]. Nearly 60% of TB patients in South Africa are HIV co-infected, and though patients receive free diagnostic tests and treatment for HIV and TB at primary care clinics, the country faces a shortage of physicians to support such care [2–5].

South Africa processes the largest number of molecular diagnostic TB assays and HIV-related tests of any country —1.2 million TB sputum tests and 3.9 million combined CD4 count and viral load (VL) tests annually [6,7]. Since 2016, national guidelines recommend that patients who are newly diagnosed with HIV should immediately receive antiretroviral therapy (ART), a CD4 count assay, and a sputum Xpert MTB/RIF test [8]. Guidelines also recommend an HIV VL test three months after ART initiation and every six months thereafter until viral suppression, at which point VL tests are reduced to an annual basis.

For each laboratory test, patients visit their clinic for sample collection and are instructed by clinic staff to return for their result after three to six working days. Patient adherence to return instructions is critical because it allows healthcare workers to promptly intervene for patients with actionable results (<200 CD4 cells per milliliter of blood, ≥400 viral copies per milliliter of blood, or a TB positive). However, 60% of VL tests have undetectable levels of HIV RNA and nearly 90% of TB tests are negative. In other words, most results are non-

actionable and do not merit an additional visit to the clinic, especially if that patient already visits monthly for ART refills. Yet patients with non-actionable results have no alternative to returning and hence, must join and contribute to the queue waiting to be seen by clinic staff [9].

Long wait times in overburdened clinics deter patients from returning and are expensive for patients who do not need to return [10, 11]. While some patients with non-actionable results may benefit from receiving CD4, VL, and TB results in-person with a healthcare provider, others may perceive that the burdens of coming to the clinic outweigh such benefits, especially if the second visit is within a few days of the first. For example, patients often pay for travel to-and-from the clinic and may also forgo paid work on the day of the clinic visit [9,12]. These and other barriers to care likely contribute to the 24% of patients with TB and 38% of people living with HIV in South Africa not being on TB treatment and ART respectively in 2018 [1,13-15]. There is an urgent need for novel interventions to provide alternative health communication options for patients, reduce unnecessary patient visits, improve responsiveness to laboratory results requiring further clinical action, and offer accessible education to patients.

A mobile health (mHealth) intervention could be a solution for improving disease management [16], especially in South Africa [17-19] where 91% of individuals own a mobile phone [20]. Previous studies in southern Africa demonstrated that delivering short message services (SMS) to patients can

improve linkage to care, retention in care, and adherence to ART and TB treatment [21-23]. Patients living with HIV in South Africa have also reported that SMS interventions were acceptable but expressed concerns about privacy and the lack of two-way communication [24, 25].

The purpose of this study was to assess MatlaMobile ("Strength by Mobile" in Setswana), an mHealth intervention to deliver CD4, VL, and TB results to patients' mobile phones. MatlaMobile used an unstructured supplementary service data (USSD) system for participants to access PIN-protected messages that, unlike SMS, were not stored locally on the mobile phone but could still be viewed repeatedly. MatlaMobile also offered options for participants to request a call-me-back from a nurse or send their laboratory result to themselves via SMS text message. We assessed whether the intervention increased participant access to their laboratory results and encouraged more appropriate follow up visits as compared to the standard-of-care. We also assessed participant satisfaction with MatlaMobile.

Methods

Study setting and design

We conducted this study in Matlosana Municipality, South Africa at one urban and two peri-urban public primary care clinics with similar numbers of HIV and TB patients. For this pilot non-randomized study, we enrolled participants into the intervention arm between June and November 2017 and into the control

arm between January and June 2018. Neither staff nor participants were masked to treatment assignment.

Study participants

In both time periods, clinic nurses referred adults (≥ 18 years of age) who had ≥1 laboratory sample taken for a CD4 count, VL assay, or TB Xpert MTB/RIF (Cepheid) to the study team. Clinic staff collected samples as part of routine clinical care. Study staff assessed eligibility of referred patients in a private room. Patients were eligible to participate if they were literate and owned or had access to a cell phone on which they were willing to receive their laboratory results. Study staff determined literacy by asking patients to read a sign in a language of their choice (English, Setswana, Sesotho, or Xhosa) and follow written instructions to draw a shape. Patients were excluded if they did not have a cell phone on their person at the time of screening. Due to low numbers of TB patients, we extended and enhanced recruitment of people receiving TB tests into the control arm. All participants provided written informed consent. This study was approved by the Institutional Review Board at the Johns Hopkins School of Medicine and the Human Research Ethics Committee at the University of Witwatersrand, Johannesburg.

Control and intervention conditions

Participants in the control arm received the standard-of-care of instructions to physically return to their clinic within 3-6 days to view their laboratory results. No mobile notifications were sent to participants in the control arm.

Participants in the intervention arm received an SMS notification on their mobile phone stating their results from MatlaMobile were available and that they could log into the MatlaMobile USSD system to view it. MatlaMobile was developed using Microsoft ASP.NET MVC technology and hosted on a shared server with a password-protected structured query language (SQL) database.

If a participant did not use MatlaMobile to see their result, study staff sent a daily SMS reminder for up to three days after the initial notification and then made two telephonic attempts to contact the participant. Study staff told participants in the intervention arm to return to the clinic if instructed to do so by MatlaMobile, rather than the standard-of-care instructions to always return within 3-6 days.

After receiving the SMS notification, participants dialed a code to connect with the MatlaMobile USSD system. USSD uses 140 character messages and is widely used in Africa for mobile banking and to purchase mobile phone call time, data, and messages. To access their laboratory result within the USSD system, participants entered a personal information number (PIN) they selected during enrollment, which was also linked to their mobile phone number. During

enrollment, study staff also provided hands-on training and verified participants could successfully log in using their PIN. We did not directly store participant PINs in the study database. Instead, we used an algorithm to hash each PIN into a unique code prior to storage. In this way, the study team never stored or had access to participant PINs.

Participants could login to the MatlaMobile system multiple times. At each login, participants selected a language (English, Setswana, Sesotho, or Xhosa) and were greeted with the following options: view laboratory result (Table 2.1), send a call-me-back request to a nurse, or view generic educational messages about each laboratory result (Table 2.2). If a participant selected the option to send a call-me-back request, the MatlaMobile system automatically sent a text message to a professional nurse on the study with the participant's phone number. The nurse responded to call-me-back requests within 24 hours on workdays.

MatlaMobile messages were based on the Health Belief Model (25). The model posits that behavior is driven by cues to action, perceived consequences, perceived benefits of acting to prevent or treat disease, barriers to acting, and one's self-efficacy. MatlaMobile messages were cues to action. The messages reminded participants that they might need to act on their laboratory results and recommended appropriate actions (e.g., "go to the clinic now"). The messages also informed participants about possible consequences ("Your results show you have TB… You can infect your family and friends."), and benefits related to

treatment (e.g., “You may need more medicine to be healthy.”). Generic educational messages and the option to speak directly with a nurse were aimed at building patient self-efficacy toward understanding their health status and how to take action.

We categorized laboratory results as either “actionable” or “non-actionable” (Table 1) based on the national guidelines at the time of study implementation. “Actionable” results included any CD4 or VL count if the patient was not yet on ART, VL ≥400 copies per milliliter or CD4 ≤200 cells per cubic millimeter regardless of ART status, or TB results positive for *Mycobacterium tuberculosis*. Messages advised participants with actionable results to return to their clinic immediately. Messages advised participants with non-actionable results that their results did not require immediate clinical action and, unless they had further concerns to discuss with a provider, they did not need to return outside regularly scheduled appointments. South African healthcare providers, in collaboration with a study nurse, developed the messages. Study staff reviewed, translated, and back-translated all messages.

Study measures

Study staff interviewed consented participants at enrollment to ascertain patient demographics (sex, age, education, household and personal income, ever ART, and whether they received HIV care at one or more clinic(s)) and clinic-level characteristics (home-to-clinic travel time and wait time at the clinic).

Staff also recorded the unique barcode of each laboratory specimen and observed the participant's phone type, either smart or basic. Smartphones are able to use mobile applications (i.e. "apps") while basic phones are typically limited to calls and texting. MatlaMobile was compatible with both smart and basic phones.

Study staff accessed the National Health Laboratory Service (NHLS) TrakCare Webview at least once daily and retrieved all available laboratory results using the unique laboratory specimen barcode and two patient identifiers (e.g. full name, date of birth, national ID). If there were near matches, study staff resolved them directly with laboratory staff who consulted original, handwritten laboratory requisition forms and the electronic Health Patient Registration System (HPRS) to check for data entry errors and alternative identifying data. Study staff also recorded the date and time each result became available in the NHLS system.

At follow up, study staff abstracted outcome data for participants using paper medical records, archived clinic files, and Tier.NET (an electronic treatment database for people living with HIV). Any time study staff entered outcome data into the study database, another staff member re-confirmed the entry against the participant's medical records for quality assurance.

The MatlaMobile system automatically collected the following user interaction metrics: language selected, date and time that messages were received and accessed, screens viewed, whether messages were viewed in part

or in full, and nurse call-me-back requests. We telephonically surveyed participants approximately one week after enrollment about their satisfaction with MatlaMobile on a 7-item scale and asked if they were aware of anyone accessing their laboratory result without their permission.

Outcomes

Our primary outcomes were whether participants, within seven days after their laboratory test was taken, 1) had seen at least one laboratory result and 2) adhered to instructions to return to clinic. In the control arm, we defined participants as seeing their laboratory result and adhering to instructions if they returned to clinic. In the intervention arm, we counted participants as seeing their laboratory result if they used MatlaMobile to view the result. We considered intervention participants to have adhered to instruction if they returned to the clinic as instructed by their MatlaMobile message.

Secondary outcomes included overall proportion of participants who returned to clinic regardless of whether the result was actionable or not, the median (interquartile range (IQR)) number of days from enrollment-to-return among those who returned within 30 days, the median (IQR) number of days from enrollment-to-return among those instructed to return, and the proportion of intervention participants who returned despite receiving all non-actionable results. We also calculated enrollment-to-return time distributions. Finally, we

described participant interactions and satisfaction with the MatlaMobile intervention.

Statistical analysis

We compared study arms using descriptive statistics. We used Kruskal-Wallis and chi-square tests for continuous and categorical variables respectively. For primary outcomes, we estimated adjusted risk ratios and 95% confidence intervals (CIs) using Poisson regression models with robust variance and controlling for participant demographics and clinic-level characteristics. For secondary outcomes, we compared proportions and means. The study was powered based on an anticipated half of the control arm having the primary outcomes, 15% loss-to-follow-up of those enrolled, and an estimated power of 80% (type 1 error of 5%) to detect at least a 15% absolute difference in primary outcomes between arms. We conducted analyses in STATA (26), at a significance level of <0.05.

Results

Screening and enrollment

Overall, we approached 630 patients and enrolled 444 participants (Figure 2.1). The primary reasons patients were ineligible for enrollment were that they did not have a mobile phone on their person (n=88) or were illiterate (n=54). Of

the 444 enrolled, we excluded 44 from the analysis for a final sample of 226 participants in the intervention arm and 174 in the control arm. We excluded participants from the analysis due to enrollment during a laboratory strike when samples were not processed between July 21 and August 3, 2017 (n=24), invalid or missing results (n=6), enrollment while the clinic offered same-day TB Xpert MTB/RIF results during a non-related research study (n=4), missing data (n=2), and other reasons (n=8).

Descriptive statistics

Median age of participants was 37 years (IQR: 32-46), and the majority were women (69%, Table 2.3). Most were living with HIV (86.5%), with a greater proportion of people with HIV in the intervention (94.8%) than the control arm (77.6%, $p<0.001$). Approximately half of participants had basic phones while the other half had touchscreen or smartphones. Overall, participants reported an hour median travel time to clinic (IQR: 0.6, 1.5) and a 3.2-hour median wait time to see a healthcare provider and receive their results (IQR: 1.6, 4.5). Participants had a total of 236 CD4, 238 VL, and 114 TB Xpert MTB/RIF assays performed, with more CD4 and VL tests in the intervention group and more TB assays in the controls.

Primary outcomes

A greater proportion of participants using MatlaMobile viewed their test result within seven days of their enrollment (73.0%) compared to the control arm (8.6%, p<0.001, Table 2.4). Controlling for demographics and clinic-level characteristics, participants in the intervention arm were 9.9 (95% CI:6.0-16.5) times more likely to view their laboratory result within seven days of enrollment as compared to participants in the control arm. Among participants instructed to return, a greater proportion of participants using MatlaMobile did so within seven days of enrollment (20.0%) than the control arm (8.6%, p=0.02). Adjusting for demographics and clinic-level characteristics, participants in the intervention arm were 3.0 (95% CI: 1.3–6.8) times more likely than participants in the control arm to return within seven days of enrollment. Stratified by type (i.e., CD4 count, viral load count, and tuberculosis), samples sizes were small and insufficient for formal hypothesis testing; however, simple proportions demonstrated a trend in favor of the intervention arm.

Secondary outcomes

A similar proportion of participants in both arms returned to clinic within seven days (8.6% v. 9.3%, p=0.82) and thirty days (28.7% v. 31.4%, p=0.84) of enrollment. Time-to-return across study arms was similar; participants in the intervention arm returned somewhat earlier (IQR: 6.5-28 vs. 6-28, p=0.04). Of the 156 participants in the intervention arm who received non-actionable results,

seven (4.5%) returned to the clinic within seven days of enrollment. Figures 1 and 2 of the Figure 2.3 describe the time distribution between enrollment-to-return among participants overall and among those instructed to return.

Interactions and satisfaction with the MatlaMobile system

Most MatlaMobile participants (88.5%) viewed their results during follow up, and of those, greater than half (64.5%) viewed results within 24-hours of availability. However, few who viewed their result also read the full USSD message (27.0%). Of all MatlaMobile logins (n=1,893), English was selected most (68.8%), followed by Setswana (15.2%), Sesotho (12.7%), and Xhosa (3.2%). A majority (95.6%) of participants signed into MatlaMobile more than once. Among the twenty-nine participants (12.8%, n=29/226) who requested a call-me-back from the study nurse, most requested help interpreting their results (55.2%, n=16/29) or navigating the MatlaMobile system (6.9%, n=2/29). Several participants (17.2%, n=5/29) selected the call-me-back option unintentionally or could not be reached by the study nurse (10.3%, n=3/29). Participants also asked when the result would be ready (3.5%, n=1/29), asked about symptoms of TB (3.5%, n=1/29), and confirmed they logged in successfully (3.5%, n=1/29).

Participants in the intervention arm were generally satisfied with MatlaMobile (Figure 2.2). Of the 159 participants who responded to the follow up survey, the majority felt their information was more protected and confidential when delivered via phone than by the clinic (95%), wanted to receive other health

information on their phone (96.9%), and preferred mobile delivery over a clinic visit to see laboratory results (96.9%). No participant reported MatlaMobile causing accidental disclosures or instances where others saw their laboratory results without permission.

Discussion

In this study, an mHealth program using USSD successfully and securely delivered CD4, VL, and TB laboratory results to patients' mobile phones in South Africa. A majority of interested patients were eligible for enrollment, and among those in the intervention arm, nearly 90% viewed their PIN-protected messages and found the program highly acceptable. This is one of the first studies to evaluate, with a separate control group, sending laboratory results using USSD directly to patients' basic and smartphones in sub-Saharan Africa.

mHealth programs using USSD systems can reach more South Africans than those relying on apps. For example, the app-based SmartLink mHealth program in South Africa piloted delivering CD4 and VL results [27]. The program excluded 90% of interested patients for not having a smartphone that could support the app with a modern Android operating system, data capabilities, and sufficient RAM [27]. In comparison, our study excluded patients only if they lacked a phone at enrollment, resulting in fewer interested patients being turned away (14%, n=88/630). USSD systems are also more accessible because they come installed on all mobile phones by default and can be freely accessed

without an Internet connection or using mobile data. In the future, mHealth programs could be made even more accessible by including voice- or image-based messages for people who cannot read or have poor eyesight [28].

This study also demonstrated that PIN-protected USSD systems are feasible and safe for delivering sensitive health information to patients with cell phones in South Africa. Although one study from Uganda suggested PINs deter patients from accessing mHealth messages [29], more than 80% of South African patients accessed their messages using a PIN in both this study and another by Maraba et al. [23]. Furthermore, no participants reported any unintentional disclosures of HIV or TB statuses in this study, the Maraba study, or the WelTel mHealth program in Kenya, which used HIV-neutral language without a PIN (30). In comparison, an SMS-based mHealth program without PINs in South Africa reported 3% (n=3) of participants having unintentional HIV disclosures [31]. Unlike SMS, USSD systems can be configured to require a PIN and do not store messages directly on patient mobile phones. Therefore, future mHealth programs should consider USSD systems, which can more reliably transmit sensitive information than SMS.

MatlaMobile and other South African mHealth programs, like MomConnect, have also been highly acceptable to patients, especially for their convenience compared to the standard-of-care [23,32]. Nearly all MatlaMobile participants (96.9%) reported they preferred to receive results via mobile phone than at clinic. These findings are further reinforced by the Maraba study, where

participants described how mHealth prevents unnecessary waiting in queues [23]. Participants in the MomConnect program also emphasized that mHealth fills a gap for rural communities that lack access to in-person services. Together, these results suggest that mHealth programs can deliver relevant health information, reduce unnecessary patient burden, and relieve clinic patient volumes. If an mHealth program like MatlaMobile were to be implemented in South Africa, however, researchers should evaluate the potential downsides of mHealth programs reducing face-to-face healthcare encounters among patients with non-actionable laboratory test results.

Finally, previous work demonstrated that nurses and patients in this specific region of South Africa are open to using mHealth for routine care [33]. Rollout, however, will require intensive patient education and engagement. For example, although nearly 90% of HIV patients in South Africa reported preferring two-way over one-way telephonic communication with healthcare providers, a minority of our and MomConnect participants requested call-me-backs [31, 34, 35]. MatlaMobile participants may not have realized there was a call-me-back service. Patient education or SMS reminders about the call-me-back feature, as done by MomConnect, could improve uptake [35]. It is also possible that the system to request nurse call-me-backs was not easy to use. Several participants unintentionally requested nurse call-me-backs, and the lowest scoring item on the satisfaction scale was, “It was easy to use MatlaMobile to connect to [the…] clinic.” This, in combination with the fact that fewer than a third of patients viewed

the full USSD message of their result, suggest that the MatlaMobile interface could be improved.

For example, future iterations should include messages that sufficiently motivate patients to return to clinic. mHealth interventions from this and the Maraba study yielded low patient return rates, despite systematic reviews demonstrating that mHealth interventions can improve adherence to health appointments and medications [27, 36, 37]. Messages may have been overly complex, since half of our nurse call-me-back requests were for help interpreting laboratory results, or inaccessible, since the target population did not contribute to writing the messages before implementing the intervention. Instead, MatlaMobile messages were designed by clinicians and revised by multiple staff members familiar with the target population. Despite this weakness, MatlaMobile offered colloquial messages in four languages each time participants logged in, whereas MomConnect only allowed users to use one language, picked at enrollment [32]. To optimize MatlaMobile, future work should examine the details of how participants engaged with the system (e.g., signing in multiple times) and work closely with patients to craft persuasive, easy-to-understand messages.

Our study has limitations. Clinics in this region primarily used paper medical records to document clinic visits. Clinic staff, who sometimes misplaced records, also did not always note when patients returned to clinic to retrieve laboratory results. This was especially true of patients whose GeneXpert tests were negative for TB. Therefore, it may be possible that our outcome data are

incomplete. To mitigate these risks, we hired trained HIV counselors familiar with the systems for filing medical records and made at least two attempts across multiple sources to retrieve each participant's record. Our study may also contain secular biases because we recruited study arms sequentially. We believe biases are minimal because we recruited participants during similar seasons and there were no major health policy changes during the study. Additionally, our telephonic acceptability survey results could include social desirability bias. The quantitative results presented here, however, align with a forthcoming analysis of qualitative interviews exploring perceptions about MatlaMobile. Self-reported data are often limited, especially for identifying breaches of confidentiality, as incidents may have occurred without the participants' knowledge.

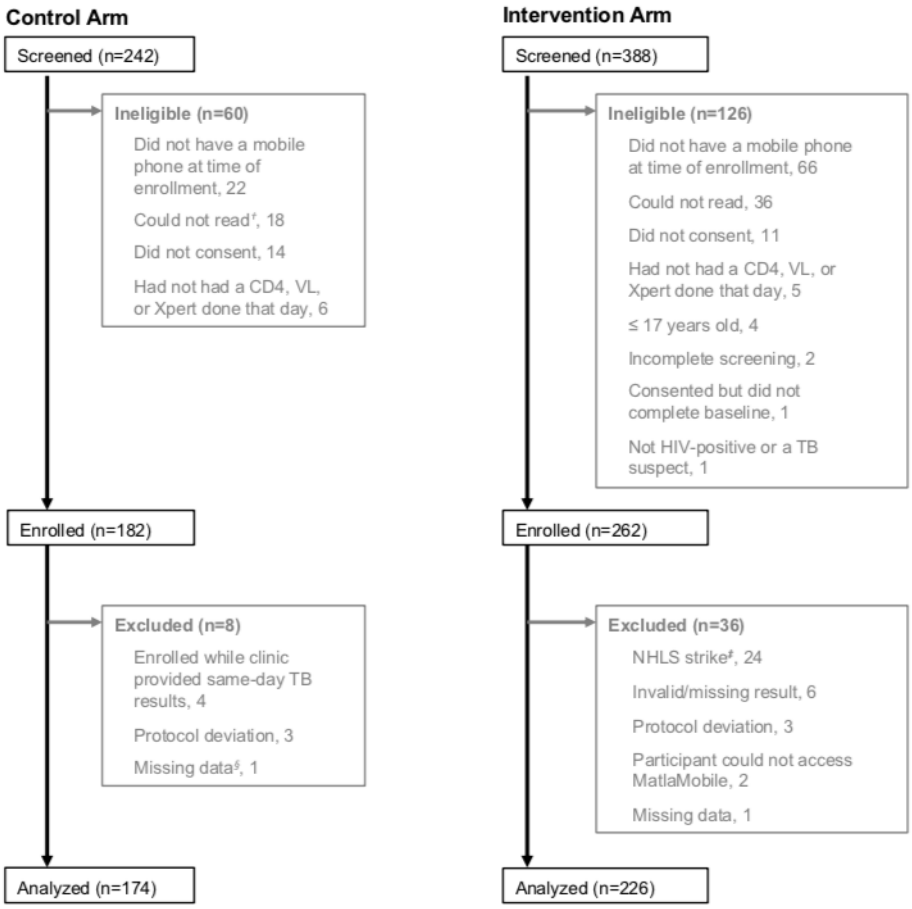
Conclusion

Results from MatlaMobile, though promising, will require further implementation research, buy-in from stakeholders, strong long-term governmental commitments, and financial investments to scale the program nationwide [38-40]. Key considerations for scaling include: patterns of SIM card and phone ownership in South Africa; potential supply chain impacts due to increased demand for ART or TB treatment; and importantly, interoperability with laboratory databases and future electronic medical records [36,41,42]. Our data suggest a USSD system is an inclusive solution to deliver results directly to patients with most types of cell phone. Therefore, a more comprehensive trial is

needed and should include an integrated version of MatlaMobile where laboratory results with improved motivational messages are automatically sent to patients [23]. Providing patients direct access to their health information can promote valuable knowledge and engagement in care.

FIGURES

Figure 2.1 – Participant screening and enrollment for the MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018)



† *Reading ability was determined by asking participants to follow instructions to draw a shape from a written sentence in a language of their choice (English, Setswana, Sesotho, or Xhosa)*

‡ *During the strike, no laboratory results were processed*

§ *One participant was missing an indication of whether they were employed and the other was missing an indication of whether ≥ 1 person in their household had an income*

Abbreviations: viral load (VL), tuberculosis (TB) Mycobacterium tuberculosis (MTB), rifampicin resistant (RIF), human immunodeficiency virus (HIV), and National Health Laboratory Service (NHLS)

Figure 2.2 – Patient acceptability of MatlaMobile and other mHealth technologies for delivering sensitive, personal health information about HIV, tuberculosis, and other health conditions (n=159) in the MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018)

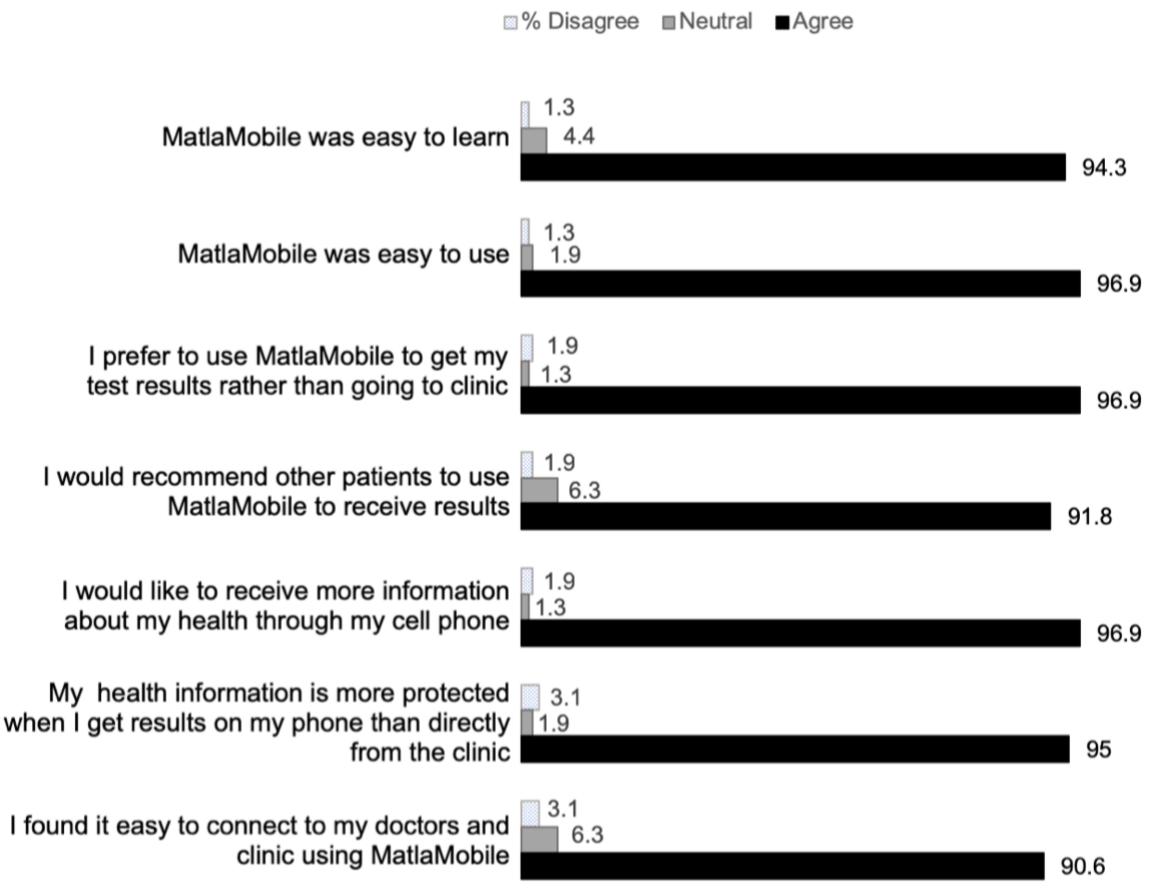
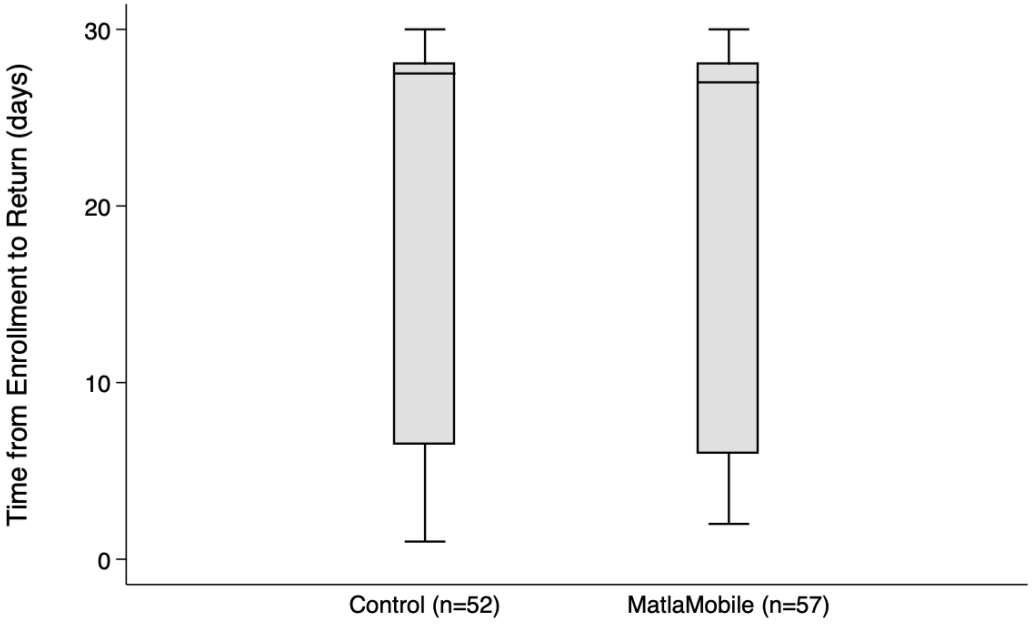
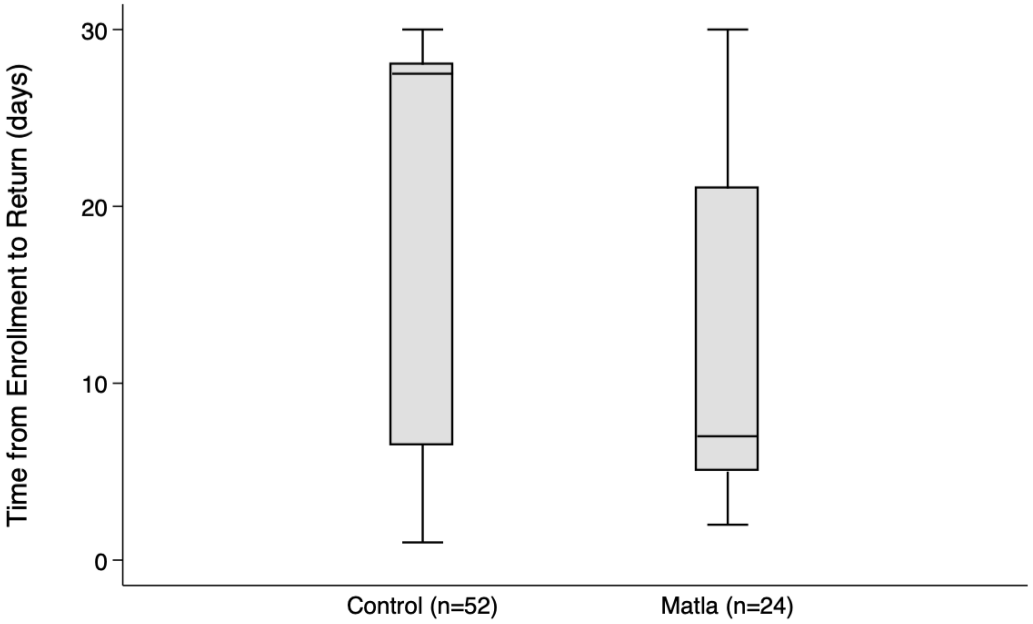


Figure 2.3 — Time from participant enrollment to return among those with at least 30 days of follow up data, regardless of laboratory result and among those instructed to return from the MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018)

A: Time from participant enrollment to return among those with at least 30 days of follow up data, regardless of laboratory result



B: Time from participant enrollment to return among those instructed to return and at least 30 days of follow up data



Our primary outcomes were “viewed results” and “adhered to return instructions” within seven days of enrollment. These were chosen based on guidelines from the World Health Organization (WHO) on digital interventions. The WHO guidelines suggest using outcomes that are proximal to the intervention — measuring reach and immediate effect. As such, we chose to measure the number of people who viewed their test result as a measure of reach. We then chose a seven-day window to assess who adhered strictly to the return instructions, even though it eliminated a majority of the participants who eventually returned for their ART.

Therefore, Figures 1 and 2 are restricted to a specific subset of participants due to limitations in our data collection protocols. Since we primarily focused on collecting sufficient follow up data to assess these outcomes, our follow up data were quite variable. We checked some participants after just 20 days post-enrollment and others 35 days afterward. Therefore, these graphs only depict participants who had at least 30 days of follow up time.

TABLES

Table 2.1 – Tailored messages delivered via an unstructured supplementary service data (USSD) system to participants in the MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018) †

Result Type	Message	Return Instruction ‡
HIV Viral Load (VL)		
Result *≥ 1000 copies / mL*	1200§ VL. High viral load means your ARV is not working or that you are not taking your ARVs every day. Go to clinic now for counseling and /// show the nurse/doctor the viral load number we sent. YOU MUST TAKE YOUR ARVs EVERY DAY. You need another viral load test done in two months	Actionable
Result *400-999 copies / mL*	500 VL. Your viral load is not completely down. YOU MUST TAKE YOUR ARVs EVERY DAY. Go to clinic now for counseling. Show the nurse/doctor /// the viral load number we sent. You will need another viral load test done in six months	Actionable
Result *< 400 copies / mL*	150 VL. Continue to take your ARVs every day to keep the virus low. Go to clinic at your next scheduled visit	Non-actionable
CD4		
Result *> 200 copies/ µL*	1200 is your CD4 count. All people with HIV should take ARVs every day. If you are not taking ARVs, go to clinic to start ARVs NOW.	Actionable if not yet on ARV; non-actionable if on ARV
Result *≤ 200 copies/ µL*	150. Your CD4 count is too low. Go to clinic immediately. All people with HIV must take ARVs every day, and you may need more medicine to be healthy	Actionable
Tuberculosis (TB)		
Result *TB Detected*	Your results show you have TB. Go to clinic NOW to start TB treatment. TB can kill you. You can infect your family and friends	Actionable
Result *TB Not Detected*	Your results show you do not have TB. If you still cough, lose weight, have night sweats, or feel sick, go to clinic for more testing	Non-actionable
Nurse "Call-Me-Back" Option (available via the main screen)		
Sends a message to the MatlaMobile professional nurse on duty	An SMS has been sent to the nurse, you will receive a callback soon	—

† *Messages displayed here as displayed on a mobile phone. "///" indicate that the characters afterwards were only available after the participant paged to a new screen.*

‡ *Actionable: participants should return to the clinic as soon as possible. Non-actionable: participants should return to the clinic at the next scheduled appointment unless experiencing continued symptoms.*

§ *Numerical results included here for illustrative purposes*

Abbreviations: viral load (VL), antiretroviral therapy (ARV), human immunodeficiency virus (HIV), tuberculosis (TB)

Table 2.2 — Educational messages available via the unstructured supplementary service data (USSD) system for intervention participants in in the MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018)

	Message
Viral Load	A viral load test checks to see how much HIV is in your blood. Antiretroviral treatment should cause a viral load result to be undetectable (<50) which means the test cannot find virus in your blood. This does not mean that you are cured, and you must continue to take your HIV medication. If you are not taking antiretroviral therapy every day or if your virus is not responding to treatment, the viral load will rise and your result will be a number that is more than 50. Viral loads of more than 1000 are very worrying and you need to go the clinic to be reassessed as soon as possible. Viral loads between 50 and 1000 need you to talk to your doctor or nurse about taking your tablets every day the next time you are scheduled to go to the clinic.
CD4	A CD4 count measures the cells in your blood that fight infection. They are sometimes called soldiers. If the CD4 count is low it means you are not able to fight infection well and may develop tuberculosis or other illnesses. The best value of a CD4 count is when it is above 500. If you are not taking antiretroviral (ARV) therapy, you must go to your clinic to start ARV. All people who are HIV positive must be on ARV medicine. If your CD4 count is below 200 you should go to your clinic as soon as possible. You may need more medicine to be healthy. If you are taking ARV your CD4 count should slowly rise up and be higher each time it is measured. If your CD4 count does not go up on ARV medicine discuss with your nurse or doctor.
Tuberculosis	The result we have sent you is for the Xpert test for tuberculosis (TB). If it says you have TB, you need to get onto TB treatment as soon as possible. If you do have TB, you have to take TB treatment for six months; if you do not take TB treatment you can infect others and your health will get worse. If the Xpert test said TB was not detected, and you still feel sick, then go back to the clinic in a day or two and ask for more testing.

Table 2.3 – Participant demographics, laboratory test used for study enrollment, and clinic characteristics of the MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018)

	Total *(n = 400)*	**Control Arm** *(n = 174)*	**Intervention Arm** *(n = 226)*	**p-value†**
Participant demographics				
Female	276 (69.0)	116 (66.7)	160 (70.8)	0.38
Age	37 (31, 46)	36 (30, 45)	38 (32, 46)	0.16
High school or higher degree	289 (72.2)	131 (75.3)	158 (69.9)	0.23
≥ 1 income stream in the household‡	297 (74.2)	150 (86.2)	147 (65.0)	< 0.001
Personally generates income§	199 (49.8)	85 (48.8)	114 (50.4)	0.91
HIV positive	346 (86.5)	135 (77.6)	211 (93.4)	< 0.001
Ever on ART	335 (96.8)	135 (100.0)	200 (94.8)	0.004
Receives HIV care at ≥ 1 clinic	41 (11.8)	10 (7.4)	31 (14.7)	0.04
Clinic Characteristics				
Peri-urban (v. urban)	111 (27.8)	91 (52.3)	20 (8.8)	< 0.001
Travel time, hours	1.0 (0.6, 1.5)	1 (0.5, 1.4)	1 (0.7, 1.5)	0.41
Queue time, hours¶	3.2 (1.6, 4.5)	3.2 (1.5, 4.5)	3.2 (1.7, 4.5)	0.54
Laboratory test done at enrollment††				
CD4	236 (59.0)	87 (50.0)	149 (65.9)	—
Viral Load	238 (59.5)	100 (57.5)	138 (61.1)	—
Tuberculosis Xpert (MTB/RIF)	114 (28.5)	69 (39.7)	45 (19.9)	—

Binary variables described as n (proportion); continuous variables as median (interquartile ranges)
† p-values computed with chi-squared test for categorical variables & Kruskal-Wallis for continuous variables
‡ One participant in the control arm did not respond to this question
§ One participant in the intervention arm did not respond to this question
¶ Duration of time from arrival at the clinic until seen by a health care provider
†† Participants could have more than one test performed at enrollment
Abbreviations: human immunodeficiency virus (HIV), antiretroviral therapy (ART), Mycobacterium tuberculosis (MTB), rifampicin resistant (RIF)

Table 2.4 – Comparison of primary and secondary outcomes between the intervention and control arms in MatlaMobile pilot trial in Matlosana Municipality, South Africa (2017-2018)

	Total	**Control**	**Intervention**	**p-value†**
	n = 400	n = 174	n = 226	
Primary Outcomes				
Viewed ≥ 1 test result within seven days after enrollment (%) ‡	180 (45.0)	15 (8.6)	165 (73.0)	< 0.001
CD4 (n = 236)	126 (53.4)	7 (8.1)	119 (79.9)	< 0.001
Viral Load (n = 238)	103 (43.3)	6 (6.0)	97 (70.3)	< 0.001
Tuberculosis Xpert (n = 114)	45 (39.4)	10 (14.5)	35 (77.8)	< 0.001
Instructed to return to clinic within seven days to retrieve their results §	244 (61.0)	174 (100)	70 (31.0)	—
Returned to clinic within seven days, as instructed ¶	29 (11.9)	15 (8.6)	14 (20.0)	0.02
CD4	20 / 148 (13.5)	7 / 87 (8.0)	13 / 61 (21.3)	0.03
Viral Load	9 / 119 (7.6)	6 / 100 (6.0)	3 / 19 (15.8)	0.16
Tuberculosis Xpert (MTB/RIF)	15 / 87 (17.2)	10 / 69 (14.5)	5 / 18 (27.8)	0.30
Secondary Outcomes				
Regardless of result, returned to clinic in…				
7 days after enrollment (%)	36 (9.0)	15 (8.6)	21 (9.3)	0.82
30 days after enrollment	121 (30.2)	50 (28.7)	71 (31.4)	0.84
Median time from enrollment to returning to the clinic regardless of result, days††	27 (6-28)	28 (6.5-28)	27 (6-28)	0.84
Median time from enrollment to returning to the clinic among participants instructed to return, days‡‡	18 (6-28)	28 (6.5-28)	7 (5-21)	0.03
Returned to clinic within seven days after enrollment, despite receiving non-actionable results only (n=156)	—	—	7 (4.5)	—

Binary variables described as n (proportion); continuous as median (interquartile ranges)

† p-values calculated using a χ^2 test for categorical variables and a Wilcoxon rank-sum test to compare medians of continuous variables

‡ Control arm viewed test results by returning to the clinic. Intervention arm viewed test results using MatlaMobile.

§ All participants in the control arm were instructed to return. Participants in the intervention arm were instructed to return if they received any actionable result message via MatlaMobile.

¶ Participants could have ≥ 1 laboratory test done at enrollment. At times, multiple results required a return visit.

†† Participants in the control (n = 52) and intervention (n=57) were only included if they had at least 30 days of follow up data and had returned within 30 days of enrollment

‡‡ Participants in the control (n = 52) and intervention (n=24) were only included if they had at least 30 days of follow up data, had returned within 30 days of enrollment, and were instructed to return to the clinic

Abbreviations: Mycobacterium tuberculosis (MTB), rifampicin resistant (RIF)

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CHAPTER 3: EFFECT OF QUANTIFERON GOAL IN-TUBE VERSUS TUBERCULIN SKIN TESTS ON THE INITIATION OF TUBERCULOSIS PREVENTIVE THERAPY AMONG PATIENTS NEWLY DIAGNOSED WITH HIV IN THE NORTH WEST PROVINCE OF SOUTH AFRICA (THE TEKO STUDY): A CLUSTER RANDOMIZED TRIAL

Abstract

Background: Rollout of tuberculosis (TB) preventive therapy (TPT) for people living with HIV (PLHIV) has been suboptimal in South Africa. We assessed whether incorporating Quantiferon Gold In-Tube (QGIT) tests into routine HIV care increased tuberculous immunoreactivity testing and TPT prescriptions.

Methods: This parallel-arm, 1:1 cluster-randomised controlled trial compared the standard-of-care (tuberculin skin tests) to QGIT. We included all clinics in the Tlokwe and Matlosana municipalities with ≥25 HIV diagnoses monthly and enrolled all consenting adult patients diagnosed with HIV ≤ 30 days from enrolment who were eligible for TPT. We highly constrained randomization to balance arms on geography and HIV care services. We used an intention-to-treat analysis for the primary outcomes: proportion of patients with a documented tuberculous reactivity result, proportion with documented TPT, and time from enrolment to outcomes. We registered with ClinicalTrials.gov (NCT02119130).

Findings: Of 15 eligible clinics, 14 were randomly assigned and one was randomly deselected. We enrolled 2,232 eligible patients between November 11, 2014 and May 31, 2017 (n=1,284, 58% from intervention clinics). At 24 months of follow-up, more participants in the QGIT arm had documented tuberculous reactivity results (69% vs. 2%) and TPT prescriptions (45% vs. 30%) than the

control arm. After controlling for baseline covariates, the QGIT arm had an absolute 60% (95% CI: 51, 68) more participants with LTBI test results and 12% (95%CI: –6, 31) more with TPT prescriptions. Among participants with LTBI test results, the QGIT arm received results faster, within a median of 6 (vs. 21) days after enrolment, than the control arm. The QGIT arm also received TPT faster (within a median of 29 vs. 54 days after enrolment).

Interpretation: Integrating QGIT into routine HIV care resulted in substantially more patients with documented LTBI test results. Furthermore, QGIT was not a barrier to TPT. Conducting QGIT regularly alongside annual active TB testing has the potential to identify and treat PLHIV who have been recently infected with TB while also reducing over-treatment of patients without TB.

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Introduction

In 2016, South Africa was home to more than seven million people living with human immunodeficiency virus (PLHIV), of whom an estimated 35 – 60% were tuberculosis (TB) immunoreactive, or presumably living with a latent TB infection (LTBI) [1–3]. Though the risk of progressing to active TB is low for immunocompetent persons, the risk for PLHIV is 30-fold that of their HIV-negative peers [4]. Active TB can have severe consequences for immunocompromised people and remains the leading cause of death for South Africans with HIV despite availability of free-of-charge TB preventive therapy (TPT) and antiretroviral therapy (ART) — both of which reduce TB incidence and mortality [5–7]. Providing TPT for PLHIV is a critically important contribution to achieving the 2035 End TB Strategy targets [8,9].

Provision of TPT to PLHIV is a multi-step process, sometimes described as a cascade-of-care. Per 2015 TPT guidelines in South Africa, nurses screen PLHIV for active TB, assess for TPT contraindications, administer a LTBI test when available, and then use a clinical algorithm to determine TPT provision and duration, from six to 36 months (Figure 3.1). The national TPT standard is isoniazid monotherapy, an inexpensive option that can be co-dispensed with ART [10].

Although the World Health Organization reported that 51% of newly diagnosed PLHIV in South Africa received TPT in 2016, this is likely a substantial overestimate [11–14]. In a meta-analysis of 15 studies, including four from South

Africa, only 41% of PLHIV were prescribed TPT [10]. Thus, despite recent research emphasis on shorter, more expensive TPT regimens to improve adherence, the majority of PLHIV are lost from care before ever receiving a prescription.

Healthcare providers in South Africa, and elsewhere, frequently cite the need for LTBI testing, especially tuberculin skin tests (TSTs), as a key barrier to TPT [15]. The test has multiple drawbacks — experiencing frequent global shortages, requiring trainings to place and interpret the TST intradermal injection, dependence on patients returning within the specified timeframe to read the result, a high false-negative rate among PLHIV, and cross-reactivity to the bacille Calmette-Guerin (BCG) vaccine, routinely administered to infants in South Africa. The difficulties of TST are compounded by excessive clinical workloads and staff shortages [16,17].

As of 2019, TST was no longer a prerequisite for TPT in South Africa [18]. However, many countries continue to rely on TST results to inform TPT prescriptions [10]. Furthermore, as South Africa begins to consider incorporating shorter but more expensive TPT regimens into national policies, there is a need to evaluate alternative tests for LTBI, which will enable an efficient use of TPT by targeting prescriptions to PLHIV at highest risk.

One alternative is the Quantiferon Gold In-Tube (QGIT) test. QGIT detects LTBI via a blood sample and has several advantages over TST. Healthcare providers do not need additional training, patients do not need to return to the

clinic, results do not rely on the subjectivity of healthcare providers, and QGIT is at least equal to TST in its performance for PLHIV with the added benefit of being agnostic to previous BCG vaccination yet strongly correlated to the risk of TB [19,20].

Therefore, we conducted a trial to assess whether QGIT, as part of routine HIV care, increased the number and speed of patients receiving a documented LTBI test result and a prescription for TPT, as compared to educating nurses on the standard-of-care (TST).

Methods

Study design and clusters

The Teko Study was a parallel-arm, 1:1 cluster-randomised controlled trial, with individual clinics as clusters. The study was conducted in the North West Province of South Africa in the adjacent municipalities of Matlosana and Tlokwe (now part of JB Marks). Ethical approval was granted by the Johns Hopkins School of Medicine institutional review board (00085133), University of Witwatersrand human research ethics committee (130609), and research committees from the North West Province Department of Health. Reporting in this publication is consistent with the CONSORT and TIDieR statements [21,22]. This trial did not require a data and safety monitoring board.

Study population

Of the 26 public sector clinics and community health centres in Tlokwe and Matlosana municipalities, fifteen met study inclusion criteria by having a monthly average of ≥25 patients newly diagnosed with HIV between August 2013 and January 2014. We randomized these clinics to receive the intervention (QGIT) or education on the standard-of-care (TST). In all clinics, irrespective of arm, clinic nurses completed clinical consultations with patients newly diagnosed with HIV and referred interested patients to the study team.

Adult patients (18 years or older) were eligible if they: had been diagnosed with HIV in the past 30 days; and self-reported that this was their usual clinic; and were not currently diagnosed with, receiving treatment for, nor had symptoms suggestive of active TB per the World Health Organization four-symptom screen [23] and were otherwise eligible for TPT (i.e., no acute and chronic liver disease, no previous history of adverse reactions to TPT, no peripheral neuropathy, and no excessive alcohol use). We did not include clinic attendees who refused consent or were mentally or physically incapable of consenting in Setswana, Sesotho, Xhosa, or English. Though national guidelines at the time indicated that patients with previous TB disease and evidence of bacteriologic cure would be eligible for TPT, few could produce documentation, so we excluded these from our analysis. HIV status was confirmed with clinic and/or laboratory records that showed at least one positive double rapid HIV test, laboratory enzyme-linked

immunosorbent assay, or detectable plasma HIV viral load (≥400 copies/ml). All participants provided written informed consent.

Randomisation and masking

An independent statistician at the Johns Hopkins Bloomberg School of Public Health randomized clinics using an electronic random number generator. We used a highly constrained randomization to allocate clinics [24]. This approach is advantageous for small trials because it simultaneously preserves the validity of the randomization while providing a near-balance between arms on covariates that will likely influence trial outcomes. In this trial, simple randomization would have yielded 3,432 possible treatment assignments. Instead, the study statistician identified 182 possible treatment assignments that would achieve balance between arms with respect to geographical location and the monthly numbers of people screened for HIV, diagnosed with HIV, and started on ART according to District Health Information System (DHIS) data. All clinics had a non-zero probability of being in the same arm as every other clinic, with the exception of two clinics in Orkney. Due to their proximity to each other, these two clinics were not allowed to be randomized into the same arm. The statistician sent clinic assignments directly to the study coordinator, who notified clinic managers of their assignment. The study team, clinic managers, and participants were not masked to clinic allocations due to the nature of the intervention but were masked to daily outcome data until study completion.

Intervention and procedures

We conducted formative research with clinical care providers and PLHIV to confirm the acceptability and appropriateness of our proposed intervention and to refine its specific mechanics [25]. In routine practice, clinic nurses draw blood to conduct a CD4 count, prior to ART initiation, for all patients newly diagnosed with HIV. In the QGIT arm, we instructed clinic nurses to also collect 1 millilitre (mL) of blood into each of three 5 mL, high altitude QGIT tubes. Drivers collected blood samples for QGIT daily and transported them to a laboratory in Johannesburg. Samples were then incubated, processed, stored, and batch-analysed approximately fortnightly according to manufacturer instructions. Drivers also delivered QGIT results to study fieldworkers as they became available, and fieldworkers inserted the hard copy QGIT results into participant medical files.

Clinic nurses in both arms also received training from a study-appointed doctor, prior to randomisation and again midway through the study. The doctor emphasized the importance of TPT and reviewed standard-of-care protocols — including placing a TST, educating and instructing patients on returning to have their TST read, interpreting the TST for PLHIV, and prescribing the appropriate TPT duration according to the clinical algorithm presented in Figure 1. In the QGIT arm, the doctor provided additional instruction on collecting blood into the QGIT-specific tubes and how to interpret QGIT results. We did not

provide any TST or TPT beyond the local supply chains, which experienced stockouts periodically.

Clinic nurses in both arms referred patients newly diagnosed with HIV to the study fieldworker stationed onsite. In the QGIT arm, study fieldworkers monitored patients for adverse events during the extra blood draws for QGIT testing. All adverse events were reported to the ethical review boards for this study. Fieldworkers explained the study to patients and obtained informed consent from interested, eligible patients and interviewed enrolled participants in a private room to ascertain sociodemographic and clinical data. This was the only contact that study fieldworkers had with participants.

All fieldworkers had ≥12 grade schooling and previous experience as HIV counsellors. Fieldworkers were trained via face-to-face instruction on good clinical practice, patient screening, informed consent, participant enrolment, interviewing, data abstraction from medical files, and QGIT laboratory results. Trainings were repeated every six months.

Approximately six months after enrolment and every six months thereafter for two years, study fieldworkers abstracted data from participant medical records onto paper study records. Separate study staff entered the data from paper into a REDCap electronic database [26]. The study coordinator resolved missing, discrepant, and invalid data queries against paper records at the clinics. Paper medical records were supplemented with three additional electronic databases: (1) Tier.net, which collects antiretroviral therapy (ART) and TPT data for PLHIV,

(2) the electronic TB disease register, and (3) the National Health Laboratory Services TrakCare Webview database, which collects HIV and TB diagnoses as well as CD4 counts and HIV viral load results.

Primary outcomes

Our primary outcomes were (1) documentation of a LTBI test result and (2) first documentation of an TPT prescription following enrolment.

Statistical analyses

We estimated that 14 clinics would provide 80% power to detect an absolute improvement of 25% or more in the LTBI test result outcome between arms of equal cluster numbers, with 40% of eligible PLHIV receiving a TST in the control arm and a significance level of 0.05. We anticipated 700 participants per arm, with 20% loss to follow-up and a coefficient of variation of 0.25 (a common default value) [27].

We described baseline demographics using crude proportions. We also calculated the crude proportion with an LTBI test administered (i.e., the patient had blood submitted for a QGIT test or had a TST placed, regardless of whether there was a documented result), a LTBI test result, and a TPT prescription, stratified by arm. We determined the proportion with each outcome, stratified by six month intervals within each clinic and overall by clinic to assess intervention

fidelity over time and by cluster. Fidelity was considered low if below 40%, moderate if between 40 to 79%, and high if 80% or higher [17].

For the first primary analyses, we used an intention-to-treat approach to calculate cluster summarized proportions for each outcome. Per our *a priori* statistical plan, we compared arms using an unpaired t-test. Unpaired t-tests are robust to non-normally distributed cluster outcomes among trials with few clusters, especially if arms contain the same number of clusters [28]. However, since normality is difficult to assess for small trials, we also conducted a nonparametric Wilcoxon's rank sum test, which does not assume a normal distribution. We compared these p-values qualitatively to confirm that the original analysis was robust to the true underlying distribution. Finally, we described the distribution of LTBI test results, the proportion receiving TPT according to LTBI status, and the proportion receiving TPT according to 2015 South African guidelines.

To attain proportion differences and ratios adjusted for imbalances in baseline covariates predictive of the outcomes, we implemented a two-stage procedure recommended by Hayes and Moulton for trials with fewer than 15 clusters per arm [28]. In the first stage, we ran multiple logistic regression models using listwise deletion of individual-level baseline demographics and omitting treatment arm to obtain covariate-adjusted residuals for each cluster. In the second stage, we used these residuals to conduct unpaired t-tests on the differences and ratios in proportions of the outcomes. For all calculations, we

accounted for clustering while computing confidence intervals. We present the empirical coefficient of variation in the control arm for comparison to the assumed coefficient in our original sample size calculations. For hypothesis testing, we assessed statistical significance according to a two-tailed p-value of 0.05.

For the second primary analyses, we calculated the median time from enrolment to primary outcomes among participants with each outcome. Because this procedure breaks randomization, we did not provide confidence intervals or p-values for hypothesis testing.

We also conducted an *ad hoc* secondary analysis among PLHIV who demonstrated early signs of being retained in care ("stayers analysis") to evaluate the effectiveness of the intervention without patient loss-to-follow-up. This population was restricted to participants who initiated ART or a had second CD4 count within 30 days of enrolment. We compare stayers to the trial population in Supplementary Table 3. We estimated the proportion of stayers with primary outcomes within 90 days of enrolment and qualitatively compared these to the full population. We chose a 90-day window because we judged it to be sufficiently long to account for nurses waiting until a patient has stabilized on ART prior to prescribing TPT and sufficiently short enough to adhere to best practices from implementation science literature, which recommend measuring outcomes proximal to the intervention [29]. We conducted all analyses in STATA, version 14.2. There was no independent data safety monitoring board for this trial

because the IRB considered the intervention minimal risk. This trial was registered at ClinicalTrials.gov, number NCT02119130.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 15 eligible clinics, 14 were randomly assigned after one was randomly deselected (Figure 3.2). All clinics remained in the study until completion. Study fieldworkers assessed 4,680 patients for eligibility at these clinics between November 11, 2014 and May 31, 2017. Of the participants screened, a total of 2,433 were ultimately ineligible. The leading reasons for ineligibility were being diagnosed with HIV >30 days prior to enrolment (n=715) and being a suspected or confirmed case of active TB (n=676). Study fieldworkers consented, enrolled, and assessed primary endpoints for 2,232 (48% of all approached) participants.

Baseline characteristics were balanced between groups (Table 3.1). Participants were a median of 31 years (interquartile range [IQR]: 25, 39). Seventy percent of participants were assigned a female sex at birth (n=1,140), of

whom 27% (n=421) were pregnant at enrolment. The geometric mean CD4 count at baseline was 286 cells/mm^3 and was similar across arms. More participants in the control arm reported being employed (51% vs. 42%) and arrived at clinic by public or private vehicle (43% vs. 26%) than the QGIT arm.

During the month prior to enrolment and up to 24 months afterward, clinic nurses drew blood for QGIT from 72% of participants in the QGIT arm and placed TSTs on 6% of participants in the control arm (Table 3.2). In the QGIT arm, intervention fidelity was generally high in the first year of the study, waned to overall moderate levels the following year with four clinics dipping into low fidelity for at least one six month period, and then reverted to moderate or high fidelity in the last six months of the intervention (Figure 3.3). The crude proportion of participants receiving a TST was the same in both arms, while only participants in the QGIT arm received QGIT. Overall, 41% of tested participants were TB immunoreactive (i.e., LTBI positive), with fewer in the control arm than the QGIT arm (33% vs. 41%). TPT was less likely to be prescribed to participants without a LTBI test, who were missing their result, or received an indeterminate result (30%) than participants who were not TB immunoreactive (i.e., LTBI negative), who were most likely to receive TPT (45%).

Overall, 35% (n=896) of participants had a documented LTBI test result (Table 3.3, Figure 3.4), with an absolute 60% (95% CI: 51, 68; p-value < 0.001) more participants in the QGIT arm (69%) than the QGIT arm (2%), adjusted for baseline covariates. In relative terms, the adjusted odds of a LTBI result was 40

(95% CI: 16, 101; p-value < 0.001) times higher for participants in the intervention versus control arm. QGIT results were documented within a median of 6 days (IQR: 3, 8) after participants were enrolled. In comparison, TST applications occurred later and therefore results were also documented later in the control arm, who waited a median of 21 days (IQR: 14, 61) after enrolment.

Overall, 37.8% (n=787) of all participants had a documented TPT prescription, with an absolute 12% (95% CI: -6, 31, p-value = 0.179) more initiating in the QGIT arm than the control arm (45% vs. 30%), adjusted for baseline covariates (Figure 3.5). The proportion of participants receiving a TPT prescription remained relatively consistent across time and did not vary substantially within each clinic (Figure 3.6). Among participants receiving TPT, the median time from enrolment to documented prescription was faster in the QGIT arm (29 days, IQR: 6, 89) than the control arm (54 days, IQR: 16, 155). P-values from rank sum tests were consistent with the unpaired t-tests for both documented LTBI test and TPT prescriptions (Table 3.4).

Nearly half (49%) of all pregnant women received TPT, with the proportion being greater in the QGIT arm (60% vs. 40%, Table 3.5). Based on the 2015 national guidelines, 67 participants would have been ineligible to receive TPT due to their CD4 count, ART status, and lack of TB immunoreactivity; yet, one in four of these participants still received a prescription.

Stayers analysis

There were 1,118 (50%) participants who initiated ART or had two CD4 assays completed within a month of their enrolment ("stayers", Table 3.6). Slightly more participants in the control arm were stayers (53% vs. 48%), with a majority of LTBI test results (99%) and TPT prescriptions (82%) occurring within 90 days of enrolment. Overall, the proportion of participants receiving a LTBI test result was similar in the overall study population and among stayers; however, stayers were more likely to receive TPT than the overall study population (56% vs. 45% in the QGIT arm; 36% vs. 30% in the control arm, Table 3.7). An absolute, adjusted 19% (95% CI: -6, 43) more stayers in the QGIT arm were prescribed TPT than the control arm (p-value = 0.12).

Discussion

In this cluster randomized trial, implementation of QGIT during a routine CD4 blood draw for newly diagnosed PLHIV resulted in 60% more receiving a LTBI test result and 12% more being prescribed TPT, compared to control clinics. TPT initiation gains were universal in the QGIT arm, with 35 to 45% of all participants receiving TPT regardless of LTBI test result. The QGIT arm also received LTBI test results and TPT prescriptions more quickly after enrolment — within a median of six days and a month respectively. The effectiveness of QGIT was enhanced after restricting the analysis to PLHIV who were retained in care, with more than half (56%) receiving TPT. These results, from a middle-

income country, both extend the generalizability of and support a previous systematic review, which found that QGIT (vs. TST) promoted the initiation and completion of LTBI testing in the United States [30]. However, our data diverged from this systematic review by also demonstrating a substantial trend toward increased TPT in the QGIT arm.

Nearly three quarters of participants in the QGIT arm received a LTBI test result, indicating that clinic nurses implemented the intervention with moderate fidelity overall. Although fidelity to QGIT waned somewhat over time, clinic nurses were substantially more likely to draw blood to conduct a QGIT test (69%) than to place a TST (2%), even after controlling for baseline imbalances between arms. Together, these results provide evidence that nurses with minimal training could feasibly incorporate QGIT into routine HIV care. However, the high levels of fidelity at the start of the intervention and then sudden increase of intervention fidelity at the end of trial suggest that oversight and integration into national policies may be necessary to sustain implementation long term.

Nurses in QGIT clinics were also more likely to adhere to national guidelines and initiate TPT for people newly diagnosed with HIV, regardless of the presence or result of a LTBI test test. TPT gains remained relatively constant throughout the study, and the median time from enrolment to a documented TPT prescription was 29 days, likely indicating that TPT was provided at a regular, monthly HIV care visit. These findings suggest that the presence of QGIT testing,

rather than a specific QGIT result, encouraged nurses to initiate TPT for PLHIV and to do so as part of routine care.

TPT initiation was even more pronounced among “stayers,” emphasizing the importance of efforts to retain PLHIV in care. Although we did not interview nurses about their motivation for increasing TPT, it is possible that they were cued to action by seeing a QGIT result in a patient’s medical records or being asked to take blood for QGIT testing [31]. Nurses may have also felt that the QGIT test fulfilled the TST requirement and were more confident initiating TPT, as compared to previous work showing hesitance to prescribe without TST [17]. However, more research is needed to characterize the understanding and influence of QGIT results in the acceptance of TPT for both nurses and patients [32].

In a recent systematic review, researchers showed that TPT benefits PLHIV on ART regardless of TB immunoreactivity, and the new 2019 South African guidelines state that LTBI testing is not a prerequisite for TPT initiation [6]. However, the benefits of TPT against TB disease for non-immunoreactive patients are likely accruing from pre-emptive treatment in a region with a high risk of TB infection. The introduction of regular QGIT testing may help prioritize TPT prescriptions by identifying recent TB infections, hence yielding maximum public health impact while minimizing individual-level burdens. Treating at the point of infection has several advantages over pre-emptive prescribing, especially in the face of the TPT shortages frequently reported in South Africa, and elsewhere,

and if the country decides to adopt shorter but more expensive TPT regimens [10,16,17,33,34]. First, PLHIV without evidence of LTBI, which was more than half of participants in this trial, would avoid unnecessary adverse events associated with TPT, which can affect up to 7% of patients on isoniazid monotherapy, the drug used in South Africa [35]. Second, it is a more efficient use of resources to target PLHIV with acute TB infections, which is when TB is at its highest risk of progressing to active disease and thus transmitting onward. Lastly, initially withholding TPT for PLHIV who are not TB immunoreactive would be especially advantageous for those with low CD4 counts who are starting ART, as they may have active TB but are not yet capable of mounting a detectable anti-TB immune response [36]. Regular QGIT testing could potentially be connected to blood drawn for CD4 assays or viral load counts during routine HIV care.

There are few studies describing the effectiveness of interventions to increase TPT in South African public clinics [30]. Previously reported interventions have been limited to the individual-level and have promoted behaviour change through efforts like training or decision-support tools [13,16,30,37,38]. Though some suggested promising results, all required intensive efforts, such as months-long clinical mentorship, and only one measured the effects post-intervention, which showed a return to pre-intervention TPT prescription levels [17,37]. Structural changes, such as integrating QGIT into

routine HIV care as done in this study, and iterative quality-improvement efforts may be required to sustain gains in TPT prescriptions [39].

There are several important limitations to consider while interpreting the results of this trial. First, study fieldworkers were present in both the QGIT and control arms throughout the intervention. Therefore, the QGIT intervention was not strictly compared to the standard-of-care but rather an educational intervention with the added capacity of a study fieldworker who was capable of HIV counselling. This may have diluted the measured impact of our intervention. Second, our estimates did not control for the numerous stock outs of TST and TPT that occurred during the trial. However, stock outs of TST was a key motivation for this trial and represents the reality of South Africa's standard-of-care. Moreover, any supply issues with TPT would have equally affected both arms. Third, our trial was limited to patients who were newly diagnosed with HIV. As such, these results may not be generalizable to people who have been living with HIV and especially not to those who have been authorized to visit the clinic less frequently but to receive multiple months of ART after demonstrating good medication adherence. Lastly, we designed this trial to minimally impact HIV care within the clinics while separately funding, transporting, and processing QGIT samples at a private laboratory. While South Africa has significant laboratory capacity for HIV-related tests, our results may not be generalizable to regions without pre-existing infrastructure or financial resources to support the addition of QGIT testing.

This study contributes additional evidence to the growing literature on the value of LTBI testing and interventions to increase TPT prescriptions for PLHIV. In summary, integrating QGIT into routine HIV care increased the number of LTBI test results and TPT prescriptions; nurses implemented the QGIT intervention with moderate fidelity. These findings suggest that, in settings with little to no LTBI testing, routine QGIT in routine HIV care may increase the number of patients who are initiated on TPT after their HIV diagnosis.

FIGURES

Figure 3.1 – South African clinical algorithm for tuberculosis preventive therapy per 2015 national guidelines

	Pregnant	Pre-ART	ART
TB immunoreactivity status			
Reactive	36 months	36 months	36 months
Non-reactive	12 months	—	12 months
Unavailable	12 months	6 months	12 months

* If tuberculin skin test is not initially available at initiation of TPT, it must be done within ONE month of initiating TPT. If patient is not TB immunoreactive, re-assess annually until it becomes positive.
ART = antiretroviral therapy. TB = tuberulosis. TPT = tuberculosis preventive therapy.

Figure 1: South African clinical algorithm for tuberculosis preventive therapy per 2015 national guidelines

Figure 3.2 – Proportion of participants receiving a Quantiferon Gold In-Tube test in the intervention arm only of the Teko randomized trial, among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

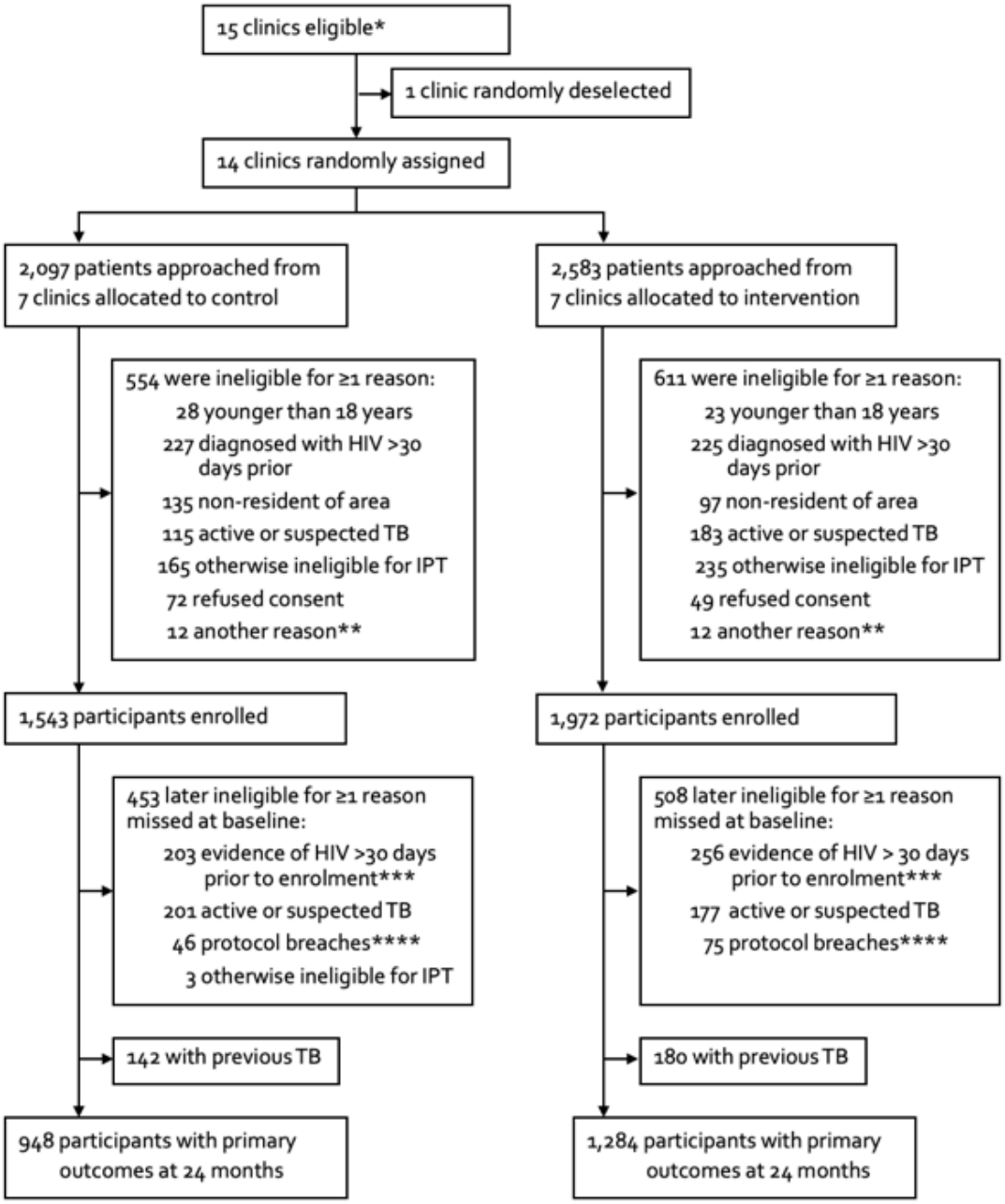


Figure 3.3 – Proportion of people with a LTBI result within each clinic of the QGIT arm in the Teko randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232). Each bar represents a six month interval throughout the trial.

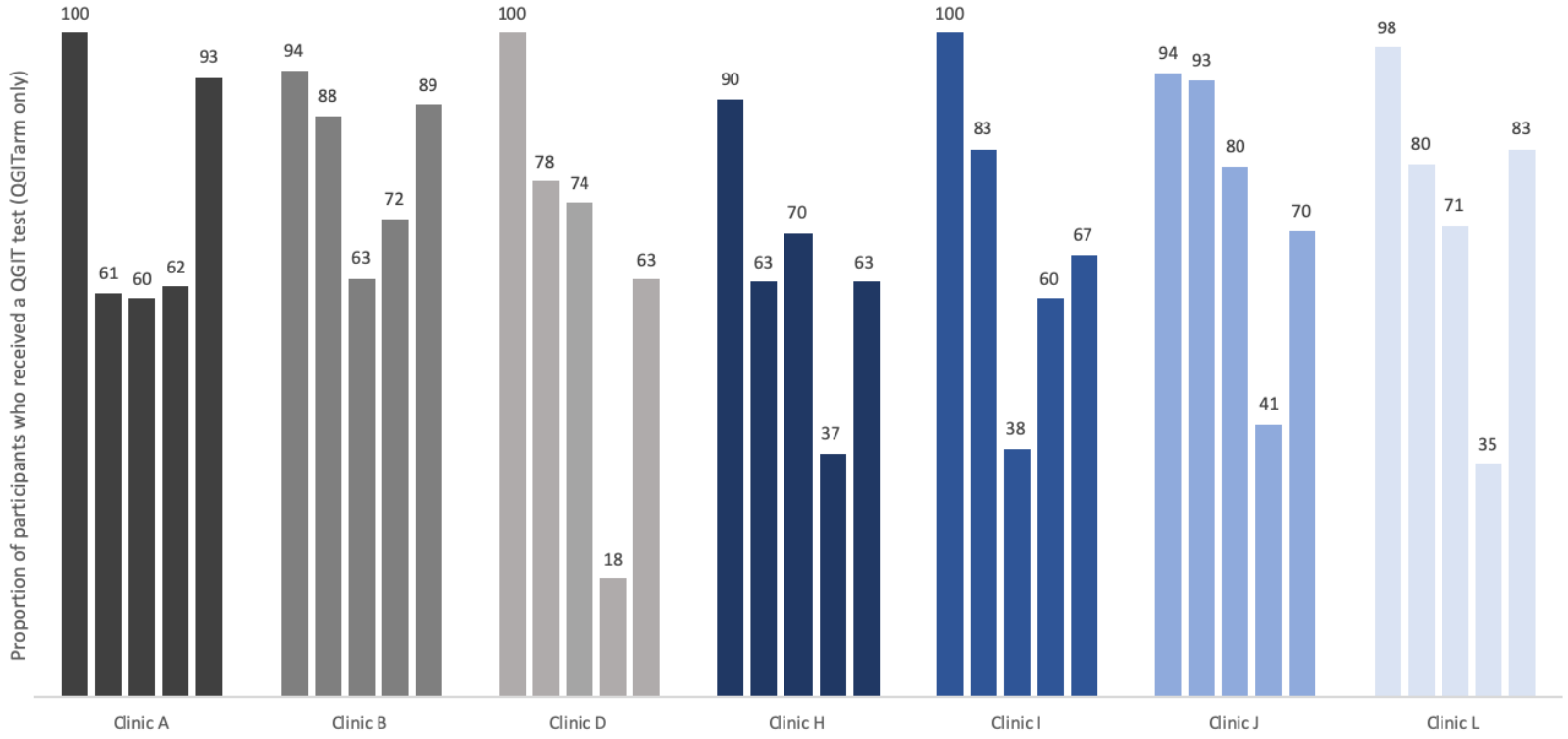


Figure 3.4 — Proportion of people with a LTBI test result within each clinic by arm of the Teko randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

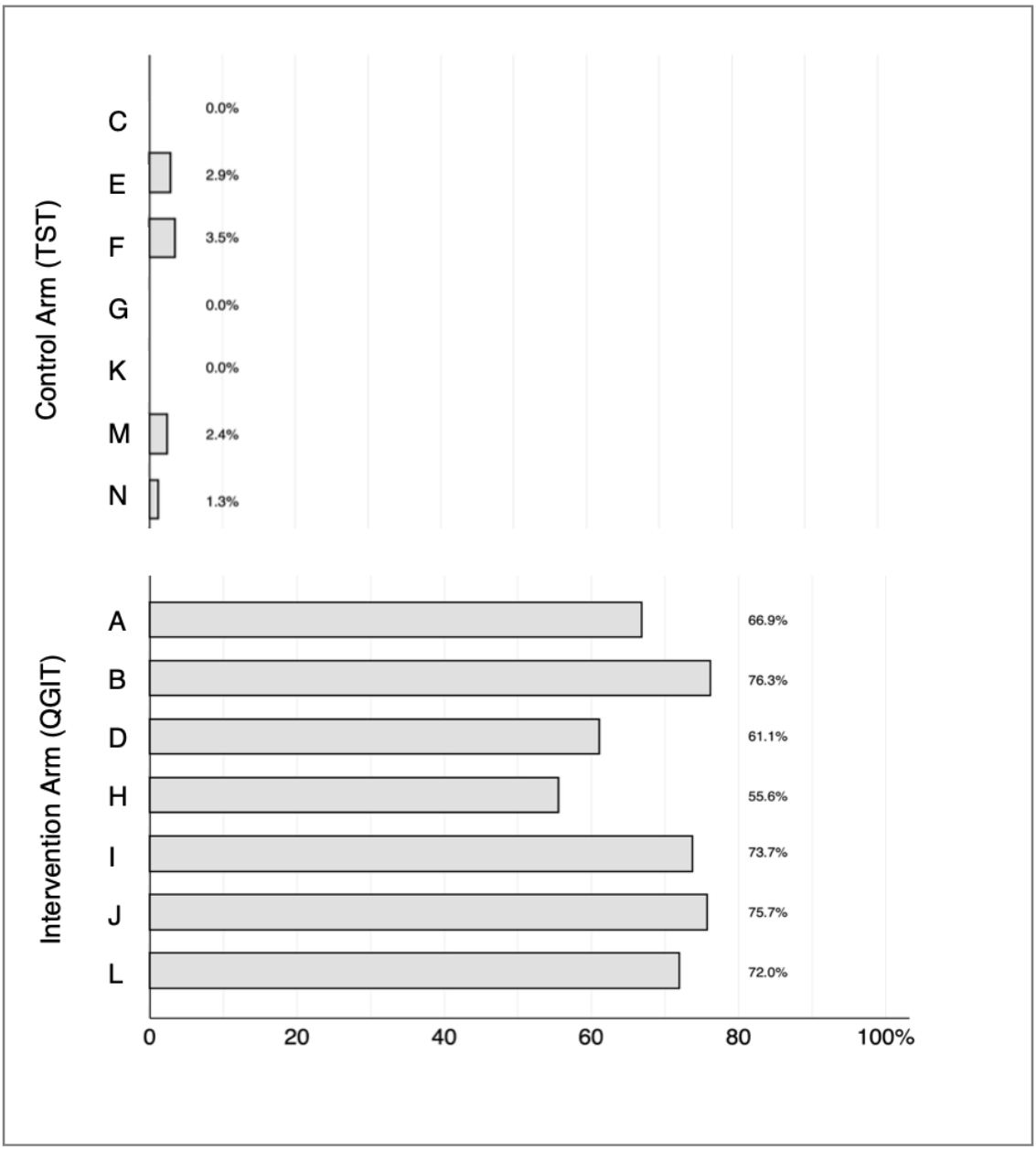


Figure 3.5 — Proportion of people with a TB preventive therapy (TPT) prescription within each clinic by arm of the Teko randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

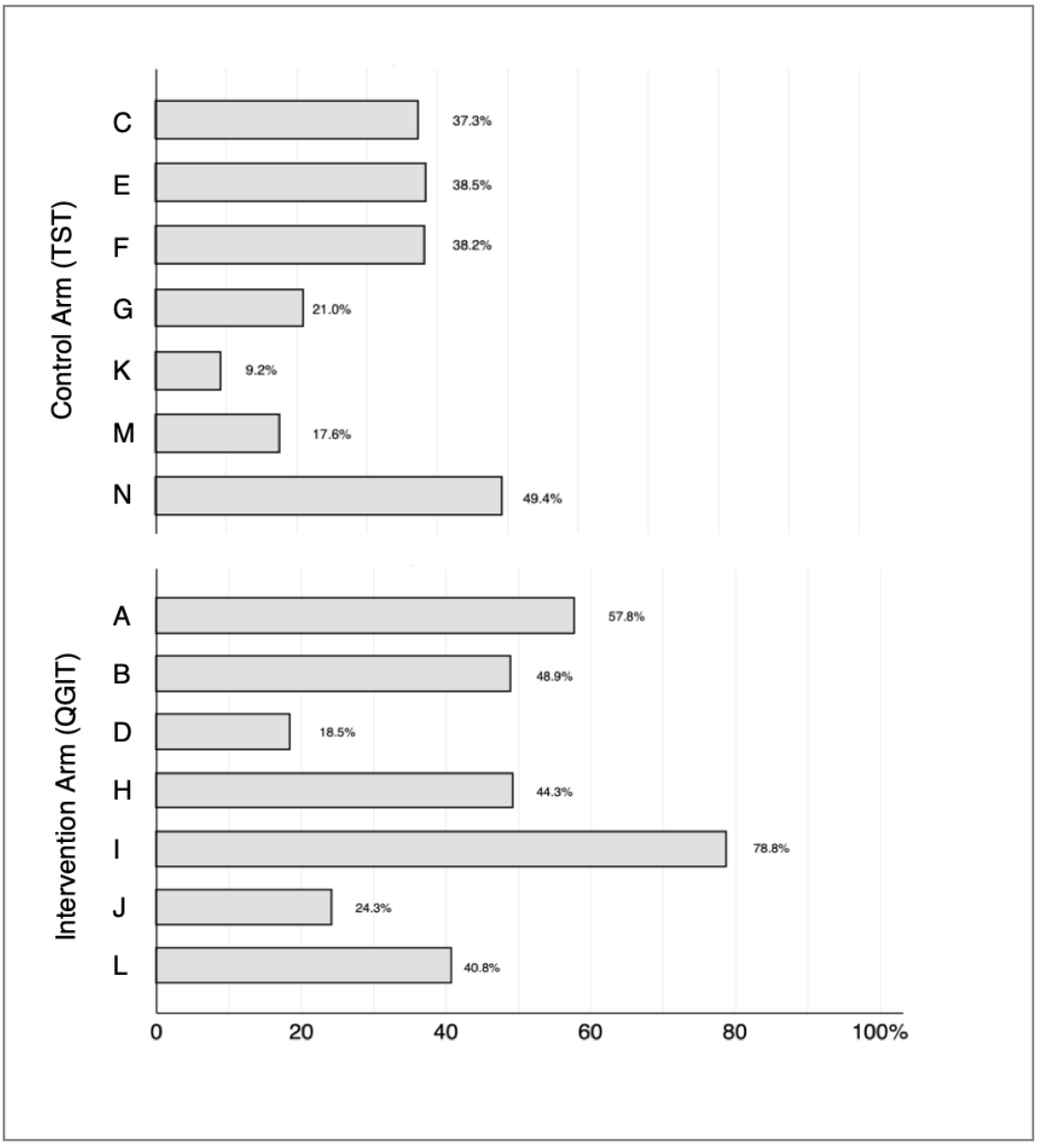
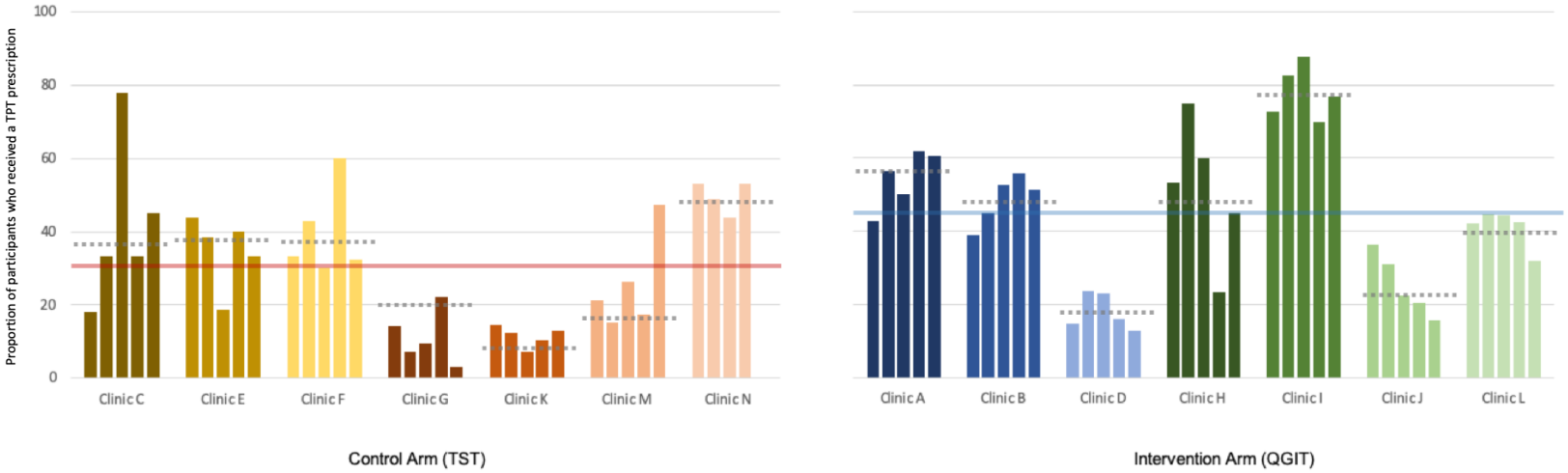


Figure 3.6 – Proportion of people with a TB preventive therapy (TPT) prescription within each clinic, by arm, in the Teko randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232). Each bar represents a six month interval throughout the trial.



TABLES

Table 3.1 – Baseline demographics from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

	Total	Control	Intervention
Clinic Level	N = 14	N = 7	N = 7
Clinics per Geographic Quadrant			
Klerksdorp East	3	1	2
Klerksdorp West	5	3	2
Orkney	2	1	1
Potchefstroom	4	2	2
Monthly mean (SD)* number of…			
New HIV diagnoses	39.8 (15.2)	24 (10.7)	21 (5.9)
Tuberculosis screenings for PLHIV	52.3 (22.3)	50.4 (21.5)	54.1 (24.5)
Antiretroviral initiations for PLHIV	22.5 (8.4)	41.8 (16.7)	37.7 (14.6)
Median (min,max) Participants per Clinic	149 (59, 289)	154 (59, 196)	144 (99, 289)
Individual Level	N = 2,232	N = 948	N = 1,284
Age (Years)			
< 20	78 (3.5%)	26 (2.7%)	52 (4.0%)
20-29	907 (40.6%)	399 (42.1%)	508 (39.6%)
30-39	715 (32.0%)	293 (30.9%)	422 (32.9%)
40-49	339 (15.2%)	138 (14.6%)	201 (15.7%)
50-59	153 (6.9%)	77 (8.1%)	76 (5.9%)
60+	40 (1.8%)	15 (1.6%)	25 (1.9%)
Sex at Birth (Pregnancy Status)			
Male	671 (30.1%)	494 (52.1%)	646 (50.3%)
Female (not pregnant)	1,058 (47.4%)	268 (28.3%)	403 (31.4%)
Female (pregnant)	421 (18.9%)	186 (19.6%)	235 (18.3%)
Female (missing pregnancy status)	82 (3.7%)	44 (4.6%)	38 (3.0%)
CD4 Count (assay result closest to enrollment, within +/- 30 days)****	286.8 (×/2.4)	289.1 (×/2.4)	285.2 (×/2.4)
Missing	153 (6.8%)	112 (11.8%)	41 (3.2%)
Education			
None	63 (2.8%)	25 (2.6%)	38 (3.0%)
Grade 0-5	204 (9.1%)	95 (10.0%)	109 (8.5%)
Grade 6-11	1,352 (60.6%)	543 (57.3%)	809 (63.0%)
Grade 12	561 (25.1%)	254 (26.8%)	307 (23.9%)
Degree/Diploma	50 (2.2%)	30 (3.2%)	20 (1.6%)
Missing	2 (0.1%)	1 (0.1%)	1 (0.1%)

Individual Level	N = 2,232	N = 948	N = 1,284
Employment Status			
Unemployed	1,209 (54.2%)	463 (48.8%)	746 (58.1%)
Employed, Student, or Retired	1,020 (45.7%)	484 (51.1%)	536 (41.7%)
Missing	3 (0.1%)	1 (0.1%)	2 (0.2%)
Monthly Income (Rand)			
0	1,294 (58.0%)	500 (52.7%)	794 (61.8%)
1 – 999	186 (8.3%)	77 (8.1%)	109 (8.5%)
1,000 – 4,999	665 (29.8%)	318 (33.5%)	347 (27.0%)
5,000 – 9,999	64 (2.9%)	38 (4.0%)	26 (2.0%)
≥ 10,000	6 (0.3%)	3 (0.3%)	3 (0.2%)
Missing	17 (0.8%)	12 (1.3%)	5 (0.4%)
Lives in house, flat, or shack	2,186 (98.1%)	912 (96.2%)	1,274 (99.5%)
Co-habitates with ≥ 1 other person	2,032 (91.2%)	857 (90.5%)	1,175 (91.7%)
Mode of transport to clinic			
On Foot (≤ 35 min)	1,106 (49.6%)	397 (41.9%)	709 (55.2%)
On Foot (36-240 min)	320 (14.3%)	101 (10.7%)	219 (17.1%)
Communal (bus, taxi)	631 (28.3%)	351 (37.0%)	280 (21.8%)
Private Vehicle	114 (5.1%)	56 (5.9%)	58 (4.5%)
Bicycle	20 (0.9%)	9 (0.9%)	11 (0.9%)
Missing	41 (1.8%)	34 (3.6%)	7 (0.5%)
Cost of transport to clinic (Rand) **	15.2 (×/1.6)	15.0 (×/1.6)	15.4 (×/1.7)
Weekly Alcohol Intake ***			
None	1,493 (66.9%)	631 (66.6%)	862 (67.1%)
Moderate	652 (29.2%)	269 (28.4%)	383 (29.8%)
Heavy	78 (3.5%)	43 (4.5%)	35 (2.7%)
Missing	9 (0.4%)	5 (0.5%)	4 (0.3%)
≥ 1 comorbidity ****	290 (13.0%)	135 (14.2%)	155 (12.1%)

* Each clinic's statistics were averaged from August 2013 to January 2014; SD = Standard deviation

** Due to non-normality, data are presented as geometric mean (x/geometric SD)

*** For males, weekly drinks between 1-13 is moderate and ≥ 14 is heavy. For females, 1-6 is moderate and ≥ 7 is heav

**** Presence of diabetes, cardiovascular disease, high blood pressure, epilepsy, asthma, cancer, or depression

Table 3.2 — Administration of tuberculin skin tests (TST), Quantiferon Gold in-tube (QGIT) tests, test results, and prescription of tuberculosis preventive therapy (TPT) from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

	Overall	Control	Intervention
By TB Immunoreactivity Test Type			
TST Administered	**138 (6.2%)**	**58 (6.1%)**	**80 (6.2%)**
Reactor	14 (10.1%)	5 (8.6%)	9 (11.2%)
Non-Reactor	35 (25.4%)	10 (17.2%)	25 (31.2%)
Missing result	89 (64.5%)	43 (74.1%)	46 (57.5)
QGIT Administered	**921 (41.3%)**	**0 (0%)**	**921 (71.7%)**
Positive	—	—	362 (39.3%)
Negative	—	—	462 (50.2%)
Indeterminate	—	—	48 (5.2%)
Missing result	—	—	49 (5.3%)
TB Immunoreactivity Tests Combined			
Administered	**1,007 (45.1%)**	**58 (6.1%)**	**949 (73.9%) ***
Result Documented **	**895 (40.1%)**	**15 (1.6%)**	**880 (68.5%)**
Positive	369 (41.2%)	5 (33.3%)	364 (41.4%)
Negative	478 (53.4%)	10 (66.7%)	468 (53.2%)
Indeterminate	48 (5.4%)	0 (0%)	48 (5.4%)
TPT Presctiptions			
TPT Prescription Documented **	**787 (35.3%)**	**271 (28.6%)**	**516 (40.2%)**
… Among TB immunoreactive	150 (40.6%)	5 (100.0%)	145 (39.8%)
… Among TB non-immunoreactive	214 (44.8%)	8 (80.0%)	206 (44.0%)
… Among TB immunoreactivity test not done, missing, or indeterminate	423 (30.5%)	258 (27.6%)	165 (36.5%)

* 52 people in the intervention arm had both a QGIT and a TST administered.

** These are crude proportions without cluster adjustment, in which the proportion is more heavily influenced by clusters with more patients.

Table 3.3 —Crude and adjusted cluster-level summary estimates of the proportion of participants with a documented LTBI test result and a tuberculosis preventive therapy (TPT) prescription from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

Arm and Clinic ID	Cluster size (N)	Outcomes (n)	%*	Unadjusted Cluster-Level Summaries (95% CI)	Adjusted* Cluster-Level Summaries (95% CI)
TB Immunoreactivity Result Documented					
TST (Control)					
C	59	0	0.00 %		
E	104	3	2.88 %		
F	170	6	3.53 %		
G	100	0	0.00 %		
K	196	0	0.00 %		
M	165	4	2.42 %		
N	154	2	1.30 %		
Total	948	15		**1.45 %**	
Median time to event (IQR)				21 days (14, 61)	
QGIT (Intervention)					
A	142	95	66.90 %		
B	139	106	76.26 %		
D	265	162	61.13 %		
H	144	80	55.56 %		
I	99	73	73.74 %		
J	206	156	75.73 %		
L	289	208	71.97 %		
Total	1,284	880		**68.76 %**	
Median time to event (IQR)				6 days (3, 8)	
			Risk Difference	67.3 (60.7, 73.9)	59.6 (50.9, 68.3)
			Risk Ratio	47.4 (20.8, 108.0)	40.0 (15.8, 101.1)

Arm and Clinic ID	Cluster size (N)	Outcomes (n)	%*	Unadjusted Cluster-Level Summaries (95% CI)	Adjusted* Cluster-Level Summaries (95% CI)
TPT Prescription Documented					
TST (Control)					
C	59	22	37.29 %		
E	104	40	38.46 %		
F	170	65	38.24 %		
G	100	21	21.00 %		
K	196	18	9.18 %		
M	165	29	17.58 %		
N	154	76	49.35 %		
Total	948	271		**30.16 %**	
Median time to event (IQR)				54 days (16, 155)	
QGIT (Intervention)					
A	142	82	57.75 %		
B	139	68	48.92 %		
D	265	49	18.49 %		
H	144	71	49.31 %		
I	99	78	78.79 %		
J	206	50	24.27 %		
L	289	118	40.83 %		
Total	1,284	516		**45.48 %**	
Median time to event (IQR)				29 days (6, 89)	
			Risk Difference	15.3 (–5.2, 35.8)	12.1 (–6.4, 30.6)
			Risk Ratio	1.5 (0.9, 2.6)	1.4 (0.8, 2.2)

Table 3.4 – P-values from unpaired t-tests and nonparametric rank sum tests to compare arms on primary outcomes from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

		Unadjusted	Adjusted (RD)	Adjusted (RR)
TB Immunoreactivity Test Result Documented	Unpaired t-test	< 0.001	< 0.001	< 0.001
	Rank sum test	0.002	0.002	0.002
TPT Prescription Documented	Unpaired t-test	0.130	0.180	0.180
	Rank sum test	0.110	0.142	0.180

Abbreviations: TB, tuberculosis; TPT, tuberculosis preventive therapy; RD, risk difference; RR, risk ratio

Table 3.5 — Proportion of participants with a documented LTBI test result and prescription for tuberculosis preventive therapy (TPT) from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

	Pregnant participants*	PLWH who should not have received ART (i.e., "Pre-ART")**	PLWH who should have received ART***	No baseline CD4 count****
	n=421	n=270	n=1,481	n=60
TB Immunoreactivity Test Resulted (and date is known)	**161 (38.2%)**	**136 (50.4%)**	**588 (39.7%)**	**11 (18.3%)**
Positive	70 (43.5%)	68 (50.0%)	228 (38.6%)	5 (45.4%)
Negative	81 (50.3%)	67 (49.3%)	326 (55.4%)	4 (36.4%)
Indeterminate	10 (6.2%)	1 (0.7%)	35 (6.0%)	2 (18.1%)
Proportion started on TPT	**206 (48.9%)**	**58 (21.5%)**	**517 (34.9%)**	**6 (10.0%)**
… among TB immunoreactive	45 (65.2%)	17 (25.0%)	88 (38.7%)	0 (0%)
… among TB non-immunoreactive	52 (64.2%)	16 (23.9%)	146 (44.8%)	0 (0%)
… among TB immunoreactivity test not done, missing, or indeterminate	109 (40.2%)	25 (18.5%)	283 (30.5%)	6 (11.8%)

* Regardless of antiretroviral therapy (ART) era and baseline CD4 count

** Per baseline CD4 count and guideline era. This group included participants with a CD4 > 350 before January 2015 or a CD4 > 500 between January 2015 and September 2016

*** This group includes anyone with a CD4 ≤ 350 before January 2015, ≤ 500 between January 2015 and September 2016, and all persons regardless of CD4 at HIV diagnosis who were enrolled from September 2016 onwards

**** This group includes anyone enrolled prior to Sep 2016 who did not have a baseline CD4 recorded.

Table 3.6 – Comparison of demographics for "stayers" vs "non-stayers" from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

	Non-Stayers *(n=1,114)*	**Stayers** *(n=1,118)*	**p-value**
Age (Years)			0.072
< 20	36 (3.2%)	42 (3.8%)	
20-29	430 (38.6%)	477 (42.7%)	
30-39	355 (31.9%)	360 (32.2%)	
40-49	184 (16.5%)	155 (13.9%)	
50-59	83 (7.5%)	70 (6.3%)	
60+	26 (2.3%)	14 (1.3%)	
Sex at Birth (Pregnancy Status)			<0.001
Male	401 (36.0%)	270 (24.2%)	
Female (not pregnant)	592 (53.1%)	466 (41.7%)	
Female (pregnant)	76 (6.8%)	345 (30.9%)	
Female (missing pregnancy status)	45 (4.0%)	37 (3.3%)	
CD4 Count (assay result closest to enrollment, within +/- 30 days)****	309.3 (×/2.5)	267.8 (×/2.3)	<0.001
Missing			
Education			0.009
None	35 (3.1%)	28 (2.5%)	
Grade 0-5	114 (10.2%)	90 (8.1%)	
Grade 6-11	694 (62.3%)	658 (58.9%)	
Grade 12	251 (22.5%)	310 (27.7%)	
Degree/Diploma	19 (1.7%)	31 (2.8%)	
Missing	1 (0.1%)	1 (0.1%)	
Employment Status			0.021
Unemployed	576 (51.7%)	633 (56.6%)	
Employed, Student, or Retired	536 (48.1%)	484 (43.3%)	
Missing	2 (0.2%)	1 (0.1%)	
Monthly Income (Rand)			0.19
0	625 (56.1%)	669 (59.8%)	
1 – 999	107 (9.6%)	79 (7.1%)	
1,000 – 4,999	339 (30.4%)	326 (29.2%)	
5,000 – 9,999	30 (2.7%)	34 (3.0%)	
≥ 10,000	3 (0.3%)	3 (0.3%)	
Missing	10 (0.9%)	7 (0.6%)	

	Non-Stayers *(n=1,114)*	Stayers *(n=1,118)*	p-value
Lives in house, flat, or shack	1,092 (98.1%)	1,094 (98.0%)	0.88
Co-habitates with ≥ 1 other person	1,001 (90.0%)	1,031 (92.4%)	0.049
Mode of transport to clinic			0.051
On Foot (≤ 35 min)	555 (49.8%)	551 (49.3%)	
On Foot (36-240 min)	181 (16.2%)	139 (12.4%)	
Communal (bus, taxi)	293 (26.3%)	338 (30.2%)	
Private Vehicle	9 (0.8%)	11 (1.0%)	
Bicycle	53 (4.8%)	61 (5.5%)	
Missing	23 (2.1%)	18 (1.6%)	
Cost of transport to clinic (Rand) **	15.5 (×/1.6)	14.9 (×/1.7)	0.37
Weekly Alcohol Intake ***			<0.001
None	689 (61.8%)	804 (71.9%)	
Moderate	370 (33.2%)	282 (25.2%)	
Heavy	50 (4.5%)	28 (2.5%)	
Missing	5 (0.4%)	4 (0.4%)	
≥ 1 comorbidity ****	149 (13.4%)	141 (12.6%)	0.59

Stayers: Participants who received ART or two CD4 count results within one month of enrolment.

* Each clinic's statistics were averaged from August 2013 to January 2014; SD = Standard deviation

** Due to non-normality, data are presented as geometric mean (x/geometric SD)

*** For males, weekly drinks between 1-13 is moderate and ≥ 14 is heavy. For females, 1-6 is moderate and ≥ 7 is heavy.

**** Presence of diabetes, cardiovascular disease, high blood pressure, epilepsy, asthma, cancer, or depression

Table 3.7 – Cluster-level summary estimates of the primary and "stayers" analyses from the Teko cluster randomized trial among people newly diagnosed with HIV between November 2014 and May 2017 in the Dr. Kenneth Kaunda district of South Africa (N=2,232)

	Cluster Summaries		Risk Difference (95% CI)		Risk Ratio (95% CI)	
	Intervention	Control	Crude	Adjusted	Crude	Adjusted
Documented TB Immunoreactivity Result						
Primary Analysis			**67.3**	**59.6**	**47.4**	**40.0**
Outcome within 2 years	68.8%	1.5%	(60.7, 73.9)	(50.9, 68.3)	(20.8, 108.0)	(15.8, 101.1)
(n=2,232)			p < 0.001	p < 0.001	p < 0.001	p < 0.001
"Stayers Analysis"			**65.2**	**59.0**	**43.1**	**38.8**
Outcome within 90 days	66.7%	1.6%	(59.3, 71.1)	(51.7, 66.4)	(19.2, 96.5)	(17.3, 86.9)
(n=1,190)			p < 0.001	p < 0.001	p < 0.001	p < 0.001
TPT Prescription						
Primary Analysis			**15.3**	**12.2**	**1.5**	**1.4**
Outcome within 2 years	45.5%	30.2%	(-5.2, 35.8)	(-6.4, 30.6)	(0.9, 2.6)	(0.8, 2.2)
(n=2,232)			p = 0.13	p = 0.18	p = 0.13	p = 0.18
"Stayers Analysis"			**20.4**	**18.6**	**1.6**	**1.5**
Outcome within 90 days	56.0%	35.6%	(-6.1,47.0)	(-5.6, 42.8)	(0.8, 2.9)	(0.9, 2.7)
(n=1,190)			p = 0.11	p = 0.12	p = 0.11	p = 0.11

Abbreviations: CI, confidence interval; TB, tuberculosis; TPT, tuberculosis preventive therapy

* Stayers: Participants who received ART or two CD4 count results within one month of enrolment.

** Adjusted for the following self-reported variables measured at baseline: age, sex assigned at birth, pregnancy status, CD4 count, highest education attained, employment status, income, homelessness, co-habitation with others, mode of transport to clinic, cost of transport to clinic, weekly alcohol intake, and presence of co-morbidities (i.e. diabetes, cardiovascular disease, high blood pressure, epilepsy, asthma, cancer, or depression).

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CHAPTER 4: PROMOTING TUBERCULOSIS PREVENTIVE THERAPY FOR PEOPLE LIVING WITH HIV IN SOUTH AFRICA: INTERVENTIONS HINDERED BY COMPLICATED CLINICAL GUIDELINES AND IMBALANCED PATIENT-PROVIDER DYNAMICS

Abstract

Isoniazid preventive therapy (IPT) reduces the risk of active tuberculosis among people living with HIV, but implementation of IPT in South Africa and elsewhere remains slow. The objective of this study was to examine both nurse perceptions of clinical mentorship and patient perceptions of in-queue health education for promoting IPT uptake in Potchefstroom, South Africa. We measured adoption, fidelity, acceptability, and sustainability of the interventions using both quantitative and qualitative methods. Adoption, fidelity, and acceptability of the interventions were moderately high. However, nurses believed they could not sustain their increased prescriptions of IPT, and though many patients intended to ask nurses about IPT, few did. Most patients explained that they did not ask for IPT due to an imbalance of patient-provider power. National IPT guidelines should be unambiguous and easily implemented after minimal training on patient eligibility and appropriate medication durations, nurse-patient dynamics should empower the patient, and district-level support and monitoring should be implemented.

Introduction

Nearly 8 million people in South Africa were living with human immunodeficiency virus (HIV) in 2020, more than any other country worldwide [0]. Among people living with HIV, the leading cause of mortality is tuberculosis (TB) [1, 2]. The World Health Organization (WHO) recommends isoniazid preventative therapy (IPT) to prevent TB in people living with HIV [3].

IPT is effective and can reduce the risk of active TB by as much as 60% among people living with HIV who have evidence of a latent TB infection [4]. The WHO currently recommends that all HIV-positive individuals without active TB in resource-constrained, high HIV- and TB-prevalence settings should be treated with 36 months of IPT [3]. In 2015, the Department of Health in South Africa rolled out national IPT guidelines based on the WHO recommendations but diverged in two ways [5]. First, a tuberculin skin test (TST) was required within one month of initiating IPT and second, patient use of antiretroviral therapy (ART) determined the prescribed duration of IPT. Despite the WHO's recommendations and South Africa's initiative to provide IPT, implementation has been slow. Less than 51% of patients newly enrolled in HIV care started IPT in 2016, and in South Africa, these numbers may be overstated [2, 6].

Since the release of the 2015 IPT guidelines in South Africa, many barriers such as including poor patient-provider communication and insufficient clinic staffing have constrained uptake [7–10]. Per previous qualitative work in in the Gauteng Province of South Africa, the most substantial obstacle for clinicians

in South Africa to prescribing IPT is a lack of confidence in their ability to write appropriate prescriptions and the treatment [7]. Interviews revealed that clinicians did not trust IPT to effectively prevent active TB. Instead, clinicians believed that IPT would be prescribed to those with active TB unintentionally and hence promote drug resistant TB. Even among clinicians who prescribed IPT to their patients, implementation was inconsistent, with some restricting their prescriptions to patients on ART or with CD4 counts below 200 cells per milliliter. Further compounding the issue, patients are rarely familiar with IPT or its benefits [7]. These barriers suggest that efforts to expand the uptake of IPT will continue to achieve limited outcomes without acceptable and feasible interventions that motivate clinicians and patients to use this critically important treatment.

In this study, we piloted a clinical mentorship intervention to improve nurse willingness to prescribe IPT and an in-queue health education intervention to improve patient awareness of and empowerment to request IPT. We chose to intervene on both nurses and patients to generate supply and demand of IPT respectively [11]. The objectives were to measure adoption and fidelity of the intervention, to assess nurse and patient perceptions of the acceptability and sustainability of the intervention, and to examine continued barriers to change.

Methods

Study setting and population

We conducted this study in peri-urban areas surrounding the city of Potchefstroom in South Africa. Potchefstroom is in the Dr. Kenneth Kaunda district, where HIV prevalence is 12.9% and TB incidence is 696 per 100,000 population [12, 13]. Unemployment in the district is 29.7%, and a minority (10%) of residents have had no formal education [14]. The district is located in the City of Matlosana Municipality, where the majority of residents speak multiple languages with the most common primary languages being Setswana (36%), Sesotho (20%), Afrikaans (17.3%), Xhosa (14%), and English (4.5%) [15].

We chose to implement our intervention in the four largest of nine public clinics — as measured by number of patients on ART in 2015 — in which there were no other ongoing IPT-related interventions. The four study clinics each had 500-600 patients on ART monthly. Three clinics were larger, with 1,000 patients on average, but had concurrent IPT-related interventions occurring and were excluded from the study. Using a random number generator, we evenly assigned clinics to receive one of the following: a nurse-centered or patient-centered intervention.

We conducted a multi-method assessment of the interventions. The quantitative assessment was conducted at a clinic level. For the qualitative assessment, we recruited all eligible, consenting nurses at clinics assigned to the nurse-centered intervention and a convenience sample of eligible patients from

clinics assigned to the patient-centered intervention. Nurses were eligible to participate if they had provided HIV care at their clinic for the past two months, were able to prescribe ART, and had participated in the nurse-centered intervention. Patients were eligible to participate if they were ≥ 18 years, HIV-positive, had received care at the intervention clinic for at least two months, and had participated in the patient-centered intervention. All research participants provided written informed consent and received 50 Rand (approximately $3.50 USD) for their time. This study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board and the University of the Witwatersrand Human Research Ethics Committee.

Nurse-centered intervention

The nurse-centered intervention promoted two target behaviors: checking IPT-eligibility for all HIV-positive patients and prescribing IPT to all eligible patients. A clinical mentor, who was a certified professional nurse with six years of previous clinical experience, led the nurse-centered intervention. The intervention consisted of six components: (1) a workshop to increase knowledge about IPT and to list clinic-specific barriers to prescribing IPT, (2) in-room consultations, (3) a workshop to select key barriers and to create an Action Plan for those barriers, (4) aid in electing and training an IPT Champion, (5) communication with the district-level TB/HIV coordinator, and (6) remote

consultations via text messaging (Figure 4.1). Details and theoretical groundings for each component are presented in Table 4.1.

In brief, the clinical mentor taught and reinforced the South African IPT guidelines in the first workshop through roleplay and brainstormed clinic-specific barriers that prevented the target behaviors (Table 4.2). In the weeks following the first workshop, the clinical mentor provided in-room consultations during the provision of clinical care to patients to model the target behaviors and to better understand clinic-specific barriers to IPT implementation. The clinical mentor then led a second workshop where nurses created an Action Plan with solutions to address clinic-specific barriers. Nurses then nominated and elected a fellow nurse to be an IPT Champion in each clinic. The IPT champion was responsible for implementing the Action Plan with help from the clinical mentor and continuing the Action Plan after the end of the intervention. For the last three weeks of the study, the clinical mentor stopped providing in-person consultations and instead contacted nurses by mobile phone through a text-messaging platform. Messages acted as a reminder to perform the two target behaviors, and offered continued, two-way communication opportunities for sustained educational and clinical support.

Patient-centered intervention

The patient-centered intervention promoted one target behavior: patients should ask a nurse about IPT. The patient intervention consisted of three

components: (1) in-person, oral health education sessions for patients waiting in the queue, (2) the provision of calendars printed with relevant health education information to incentivize participation in those education sessions, and (3) posters in each clinic prompting HIV-positive patients to ask their nurses about IPT. To design the materials, we used prior findings from this province on patient barriers and facilitators to IPT [16]. Before the start of the study, we also conducted two formative focus group discussions with twelve total patients from the patient-centered intervention clinics to solicit feedback on initial drafts of the materials. The final patient-centered intervention incorporated this feedback prior to implementation.

Each clinic had two queues in separate spaces. One queue was for chronic care and the other queue was for maternal and child care. The median queue time in similar, neighboring clinics was 3.2 hours (interquartile [IQR]: 1.6 – 4.5 hours), with the vast majority of patients arriving in the morning (unpublished data). To educate all patients regardless of arrival time, we conducted two sessions for both queues, once in the morning and again in the afternoon, for a total of four sessions daily per clinic.

Health education sessions reviewed HIV symptoms, transmission, prevention, and treatment; TB symptoms, transmission, prevention, and treatment; differences between latent TB infection and active TB; purpose and benefits of IPT; and encouragement for patients to ask nurses about IPT. Assistants conducted the oral health education sessions in Setswana, Sesotho,

English, and/or Xhosa depending on audience makeup and repeating in different languages as needed. Assistants distributed 2,839 calendars across 3,176 non-unique attendees, as some patients both attended and were counted in multiple sessions. Assistants offered all patients at least one calendar. In an average education session, research assistants spent 4.5 minutes teaching, 9.5 minutes engaging patients with questions and distributing calendars to those who responded, and 1.3 minutes distributing calendars to the remainder of patients at the end of each session.

Two South African research assistants conducted the health education sessions, aided by large visual depictions of key concepts. Both had Bachelor's degrees in psychology and were specially trained on the epidemiology of TB and HIV, the health belief model [17], national guidelines for prescribing IPT [5], and audience engagement techniques.

Data collection

For the quantitative assessment of the study, the clinical mentor took attendance after interacting with nurses in workshops or in-room consultations. Research assistants recorded the number of patients who attended each in-queue education session.

For the qualitative assessment of the study, a female researcher from South Africa made in-person requests for interviews with all eligible nurses in nurse-centered intervention clinics. The qualitative researcher also made in-

person requests for interviews with a convenience sample of patients who had just finished listening to the in-queue education session at patient-centered intervention clinics. We recruited patients until we reached data saturation [18]. The qualitative researcher conducted and audio recorded face-to-face, in-depth interviews with nurse and patient participants in local languages in which interviewees were fluent (English, Setswana, and Sesotho). The researcher administered a short demographics survey to participants and then used semi-structured interview guides to explore knowledge about and the acceptability of IPT. The qualitative researcher had no prior relationship with any nurse or patient and conducted interviews in a private clinic room. Immediately after each interview, the qualitative researcher summarized key findings into memos. Audio recordings were translated and transcribed into English, returned to the nurse participants to verify accuracy, and de-identified for data analysis. In the last month of the study, the lead author also conducted informal debriefing sessions with nurses at all four clinics.

Outcomes

There were four implementation outcomes: adoption, fidelity, acceptability, and sustainability. For the quantitative assessment, we measured adoption of the nurse-centered intervention and fidelity of the patient-centered intervention. Adoption is the uptake of the intervention, and fidelity is the extent to which the intervention was implemented as initially planned [19]. For the qualitative assessment, we gauged participant perceptions about the acceptability and

sustainability of the interventions. Acceptability describes whether a stakeholder finds a practice to be “agreeable, palatable, or satisfactory,” and sustainability relates to whether a new behavior will be maintained during normal clinic operations [18].

Statistical analysis

We calculated the adoption of the nurse-centered intervention as the proportion of nurses who attended the mentor-led workshops and consented to have in-room consultations. We measured the fidelity of the patient-centered intervention as the total number of education sessions performed as a proportion of the targeted four sessions per clinic for each of the 67 working days spent on site. Adoption and fidelity were considered low if below 40%, moderate if between 40-79%, and high if 80% or above, based on cut-offs from previous health education interventions from the implementation science literature in resource-constrained settings [20–23].

We assessed the acceptability and sustainability of the intervention using thematic analysis of the in-depth interviews [24]. Two research assistants coded the transcripts by hand with pre-specified codes (barriers to the targeted behaviors and what made each intervention acceptable or sustainable). The lead author (BAJ) then read the transcripts line-by-line, coded them with the same pre-specified codes in Atlas.ti (version 1.0.50), and open coded emergent concepts. The qualitative researcher, research assistants, and lead author

discussed these themes to ensure that they were inclusive of all participant interviews. While re-reading coded extracts and interviews, the lead author further revised and refined codes into themes in a way that incorporated disconfirming evidence. Themes were iteratively refined in conversation with co-authors through grouping, drawing connections, and evaluating frequency and saliency. The lead author then checked the final themes by re-reading all coded extracts and interviews. The lead and second authors selected quotations primarily on the basis of representing key themes and using an iterative process of peer debriefing.

Results

Descriptive statistics

From October 2016 through February 2017, we approached thirteen nurses and eleven patients to participate. We were unable to interview three eligible nurses due to scheduling conflicts; one patient was ineligible because of being HIV-negative. In total, we interviewed 10 nurses and 10 patients (Table 4.3). Interviews were a median of 30 (IQR: 27-33) minutes with nurses and 15 (IQR: 15-19) minutes with patients. On average, nurses had been practicing at their current clinical level for 5.9 years (standard deviation [SD] = 4.1), had been working in their clinic for 4.6 (SD = 3.6) years, and were 37.2 (SD = 9.6) years old. Patients were diagnosed with HIV an average of 5.5 years (SD = 4.2) prior to enrollment and were 34.9 (SD = 11.7) years old.

Adoption and fidelity

Adoption of the nurse intervention was high, with twelve of thirteen eligible nurses attending both training workshops (92.3%). Additionally, the clinical mentor provided a total of 38 in-room consultations across all 13 eligible nurses, each lasting an average of 80 minutes. Fidelity to the patient intervention was moderate, with research assistants providing 167 of the 268 (62.3%) planned education sessions.

Acceptability: Nurse intervention

Overall, nurses described the intervention as acceptable and many expressed a desire for it to continue. Nurses particularly enjoyed the participatory aspects of role-playing patient scenarios, developing clinic-specific Action Plans, and learning about one another's challenges in caring for HIV-positive patients. Nurses expressed that two aspects of the training were particularly critical for motivating change: first, the clarification of national guidelines and second, the external oversight from the clinical mentor.

Utility of workshops to clarify ambiguous national IPT guidelines

Nurses unanimously described the South African national IPT guidelines as ambiguous, confusing, and incomplete. As a result, a majority reported having

no practical experience applying the guidelines in a clinical setting. For example, one nurse commented that although she had placed a tuberculin skin test (TST) at a regional training, she had never done the test on a patient in her clinic and was unsure whether she could read the result.

Nurses were also unsure whether they could initiate a patient on IPT without placing a TST and how the prescription duration — which can span from six months to three years — was impacted by patient age, pregnancy, antiretroviral status, and results from the TST. Nurses pointed out that although the national guidelines instruct them to prescribe IPT even if TST is out of stock, the guidelines also state that a TST must be placed one month after IPT initiation. The guidelines have no instruction of what to do if TST remains out of stock after IPT initiation. Nurses said that this feeling of uncertainty and ambiguity of guidelines sometimes prevented them from prescribing altogether:

> *"Previously we were not sure… now there are [IPT durations of] three years... one year. We were all not sure for how long... We thought rather than making mistakes, let's not give it out. But now [that we've completed the workshops] there is a change." (Nurse 007)*

Speaking to the effects of the intervention, the same nurse explained this "change" at another point in the interview as "having light." In this instance, "light" was a reference to gaining a more practical understanding of how to follow the

IPT guidelines and how those guidelines fit into pre-existing clinical practice for HIV patients. In particular, this nurse said she and her colleagues were unsure how to determine the length of time that a patient should be on IPT.

Another nurse echoed this sentiment by explaining that the workshop had motivated her to prescribe IPT by providing a full understanding that included the how and why of IPT:

> *Interviewer: "What is it that … is pushing [the other nurses] to initiate more IPT?"*
>
> *Nurse: "We are doing something that we know. That you understand clearly. It can do wonders. I really like to do things that I know, especially nursing. Yoh! It's not easy to just say, 'I will... give [IPT…or just a medication] because they said we must give.' That's what happened previously." (Nurse 008)*

This quotation reveals that this nurse also had difficulty complying with the national guidelines based on incomplete knowledge. She found the workshop useful because it addressed a gap in that knowledge while also going beyond to emphasize the importance of IPT for HIV-positive patients and hence helped change her behavior.

Benefit from external oversight from the onsite clinical mentor

In addition to describing the utility of clear information, nurses recounted motivation coming from a variety of sources. Some nurses, like the one quoted above, were intrinsically motivated to practice something they perceived themselves as fully grasping. Other nurses said the IPT Champion motivated them with encouragement and weekly announcements at group meetings. Most of all, nurses and the IPT Champions reported being most motivated by the presence of the clinical mentor. Nurses specifically appreciated that the clinical mentor did not chastise them or demand changes without reason. Instead, the clinical mentor gently emphasized looking at the protocols whenever there were deviations:

> *"She will just do a check and say, 'Oh sister, didn't you forget this and this' and then we go back to the protocol together. You'll see that? There? This is the real nurse because the protocols are really actually what we are required to use." (Nurse 008)*

Despite the importance of the clinical mentor, most nurses were initially uncomfortable with her observing their work. This anxiety subsided for all but one nurse, who stated that her work with patients was obstructed due to the clinical mentor's presence:

"The patients... are not used to her. When they see her in the room, some do not feel free... I have noticed that some of them when she is here, they are not open. I am mostly working with TB and HIV patients... But when I am with someone, they will be quiet, and that doesn't give me the chance to acquire more information that I need..." (Nurse 002)

When this nurse suspected that certain patients might not be willing to disclose relevant medical information in the presence of the clinical mentor, she asked to have in-room consultations on a different day. The nurse stated that she still consulted the clinical mentor for clarifications about IPT.

Acceptability: Patient intervention

Patients approved of the education session content and said it was acceptable to provide HIV-related education to the entire queue, so long as it did not reveal their status to others. Patient interviews demonstrated that the intervention had heightened awareness around HIV and TB but did not effectively aid patients in retaining significant information about IPT. For instance, five out of ten patients — three IPT-naïve and two patients who had previously taken IPT — knew that IPT prevented TB disease. One of 10 patients could recall the full name of the therapy (i.e., isoniazid) or its acronyms (i.e., IPT or INH). After hearing the session multiple times, later patient interviewees demonstrated

somewhat better recall, suggesting that repeated education sessions enhanced patient knowledge.

Beyond the sessions themselves, the calendar incentive for participating in the education session was particularly well received. Patients expressed appreciation for its depiction of a local monument and acting as a way for patients to remember their appointments. Every patient interviewed said they would hang the calendar in their home and would share what they had learned with their close family and friends, a sentiment captured by one participant who said:

> *"There is no way that I cannot share it with others. It is also important to share for those who are not living with HIV as well. To share knowledge that TB is real, and you can live with it. You can be on treatment for certain periods and get well again. I will [also] share the light on TB symptoms..." (Patient 002)*

Despite an apparent willingness to hang the calendar in their home, no patient indicated full awareness of its content about HIV, TB, and IPT. In comparison to the calendars, no patient mentioned the posters unprompted, and when prompted, many said they had not seen the posters or were, as one patient said, "not paying any attention to them."

Finally, though patients reported being more prepared to have a conversation with their provider about IPT, many patients stated they were still unsure of how to begin. In the patient-centered intervention clinics, discussion with nurses revealed that there had been few requests for IPT. A lack of requests indicated that despite patient acceptability of the intervention, barriers remained for patients to bridge the gap between intending and enacting the target behavior.

Sustainability

Both nurses and patients living with HIV expressed that their intervention was overall acceptable and had provided them with sufficient knowledge about IPT. Despite this, almost every interviewee stated that the intervention alone could not achieve or sustain sufficient change. Two common reasons surfaced across interviews. First, nurses and patients stated that the individual is responsible for acting after being informed about IPT:

> *"I think that you [outside researchers] can only do things up to a certain standard... the source of motivation comes from an individual self. So, there is not much you can do, with regard to trying to motivate somebody." (Nurse 001)*

"I don't know exactly what is it that you can do [to help me talk with the nurses about IPT] ... it's for us to be equipped with the knowledge about IPT while we are at the clinic. From there, it is my duty to decide to go and tell the nurses that I need IPT that I heard about." (Patient 005)

Second, even when motivated to enact the target behaviors of asking about and prescribing IPT, patients and nurses described the opposite party as resistant to change. For instance, nurses said that patients misunderstood or were unwilling to cooperate with an IPT prescription, as exemplified by one nurse who said:

"I have already received back the IPT from two of my clients... I gave them education and when the community health workers visited, [the patients] returned the IPT – saying that they don't need it anymore because they don't have TB..." (Nurse 002)

Patients, in turn, said they were often intimidated during their conversations with nurses. Patients expected nurses to initiate and explain new medications as needed. Of the ten patients interviewed, one reported asking a nurse for IPT during an appointment. The patient described being incorrectly denied an IPT prescription because the nurse told them that they "did not have TB."

The remainder of patients stated that they intended to ask about IPT but could not find a platform. Although patients said most nurses were approachable, nearly half reported that nurses were sometimes rude, and that this discouraged patients from asking about IPT. As one patient said:

> *"Honestly, you get different types of nurses here. You get types that when [they] know that you are an HIV patient… some have like an attitude towards you. And then you will get some that tries to be nice to you. So, sometimes you don't even know if you should ask the question or if you shouldn't ask the question. It is like you are being inconvenient... If I see that you have an attitude, I won't bother even asking. I'll rather wait for someone else who is more willing to work with me and be friendly. Someone that I can see and can ask you questions because you really want to help me." (Patient 008)*

In addition to the above barriers mentioned by both nurses and patients, nurses pointed to several clinic- and district-level barriers that would impede long-term change. First, in the absence of external oversight, nurses said that the IPT Champions would stop their work and nurses would lose their motivation to prescribe IPT:

"I think you must keep on visiting us, keep on giving us information… Check whether are we still on the right track or are we doing the right thing. You shouldn't just come once... and think that we are still doing it." (Nurse 002)

Some nurses said that the IPT Champion alone was not enough motivation and suggested that the effort might be better sustained with refresher trainings, support, and oversight from district-level management. Others suggested that text messages could mitigate a decline in motivation. For example, one nurse agreed the intervention could continue to be effective from afar:

"They sent us... SMSes [so] we will continue to remember that there is IPT. We have to continue. If I miss some points during training, I'll be able to know from those SMSes and scenarios that... ohhh! When the pregnant women come.... I have to do this and that." (Nurse 010)

This quotation demonstrates that the text message scenarios provided continued educational opportunities and were also a convenient touchstone for guidance on the appropriate care for different patient scenarios. In the absence of face-to-face clinical mentorship, the messages also reminded the nurses to continue practicing the national guidelines. Though text messages were

generally found to be acceptable, nurses did not want to receive messages outside of work hours.

Other clinic-level barriers to sustained progress included IPT prescriptions outpacing incoming inventories of isoniazid and accompanying medications, resulting in district-wide stockouts. While Action Plans had arranged to increase IPT inventory at each clinic, the intervention had not considered the larger system. Nurses also frequently mentioned that disorganized patient charts and the lack of an IPT-specific log were significant barriers to patient continuity of care. Though there had previously been a district-wide IPT log, there had been recent national changes that removed them from the clinics. The intervention did not provide a way for nurses to easily track each patient's progress toward their prescribed IPT duration, and without a log, most nurses stopped patients who had been initiated to avoid the possibility of prescribing IPT past the intended duration. Failure to maintain records also meant that data were not captured correctly, and improvements in IPT prescriptions were not accurately reflected at group meetings. Finally, nurses repeatedly stated that staff shortages and a large patient burden prevented them from screening every HIV-positive patient for IPT eligibility.

Discussion

This study assessed the adoption, fidelity, acceptance, and sustainability of two interventions for increasing the prescription of IPT to eligible people living with HIV. The nurse-centered intervention had high adoption, and the patient-centered intervention was implemented with moderate fidelity. Nurses and patients both reported that the interventions were acceptable. Despite positive implementation outcomes, this study revealed that participants did not describe themselves as fully capacitated or motivated to sustain the behavior changes their interventions aimed to achieve. Furthermore, gains from the nurse-centered intervention were perceived as unsustainable and beyond each clinic's capacity without district-level changes.

Both nurses and patients pointed to one another as reasons that IPT prescriptions were not being fully achieved, which is a common phenomenon in interventions requiring the cooperation of multiple parties and akin to self-motivated attributional biases [25, 26]. Both patients and clinicians in this and other studies in South Africa, though, generally perceived clinicians as the party controlling patient care [7, 27]. This squarely places the onus on clinicians to promote IPT and on the health system to provide unambiguous guidelines and effective training to clinicians.

Though patients in this study found the intervention acceptable, few enacted the targeted behavior of asking a nurse whether IPT was right for them.

Patients described uncertainty in how to begin the conversation or whether to offer their opinion, indicating a lack of agency or perceived behavioral control over their care [28, 29]. To improve the implementation of IPT in the Northwest Province, patients suggested changing patient-nurse communication to empower the patient.

Patient-centered communication is one option for nurses to shift the power dynamic and enable patients to more actively engage in their care [30]. For example, nurses could communicate in a way that shares power and responsibility with their patients by eliciting patient ideas or expectations. This type of communication may encourage some patients to ask about IPT, but previous work in South Africa regarding IPT promotion indicates that many patients do not ask questions since they believe that providers act in their best interests [27]. This is bolstered by a separate study regarding patient preferences for communication styles in Mali, which showed that although a substantial proportion of patients surveyed (40.2%) preferred *sharing* power with their provider, a similar proportion (35.8%) still preferred healthcare workers to lead the interaction; however, nearly a quarter had no preference (24.1%) [31]. Therefore patient-centered communication and education alone will not sustain IPT initiation. Proactive clinical action will be required.

Clinical education and training are essential to successful rollouts of any new medical guideline. The nurse-centered intervention in this study was moderately successful and motivated some nurses to perform the targeted

behaviors. Nurses required intensive clinical training because the current IPT guidelines are neither easily nor quickly understood. Our data reinforced findings from a 2010 study in South Africa that uncertainty about the national guidelines and lack of experience prescribing IPT are major barriers to the uptake of IPT among clinicians [7]. Our study showed that an educational intervention may instill confidence in nurses to act if it (1) uses active learning techniques to introduce concepts, (2) shares the "light," i.e. clarifies any ambiguities remaining after initial training sessions and emphasizes why IPT is important for patients living with HIV, and (3) reinforces learning using onsite clinical mentorship that both encourages action among hesitant nurses and supports the efforts of nurses already acting.

Nurses unanimously expressed concern, however, about the sustainability of the intervention and how they would maintain their new behavior. Similar to other nurse-education interventions to improve TB care elsewhere in South Africa [32–34] and sub-Saharan Africa [35], our study showed that onsite clinical mentorship may inspire short-term but not long-term change among nurses. Text messaging was one acceptable option for offering continued support. Such digital interventions, with a large reach but little effort, are especially promising in South Africa, which faces a severe shortage of healthcare workers including nurses [9, 10].

Beyond wanting continued clinical mentorship, nurses emphatically expressed a need for district-level initiatives to improve methods of stocking IPT

sufficiently, monitoring individual IPT prescriptions month-to-month, maintaining reasonable nurse-to-patient ratios, and sustaining motivation to prescribe. These needs are similar to those reported from PALSA PLUS and NIMART, two successful training initiatives in South Africa that task shifted the diagnosis and treatment of TB and HIV to nurses in 2004 and 2011 respectively [36–38]. The success of these programs was heavily facilitated by district-level HIV and TB coordinators who mitigated system-level barriers. For example, during the PALSA PLUS rollout, coordinators initiated operational changes with clinic managers and found nurses to fill vacant positions [36].

This study had several limitations. First, the small number of clinics sampled may have prevented us from attaining sufficient levels of facility-specific variations for proper saturation of themes. Second, this work was conducted in clinics in townships, and the results may not be transferable to other regions of South Africa or the world. However, the rich description of findings makes the findings transferrable to other studies of nurse and patient perspectives on disease management in similar contexts. Finally, while interviewer effects (e.g. social desirability bias) may have influenced participant responses and analytic processes (e.g. confirmation bias) may have influenced the results, the following steps were taken to improve the credibility of these findings: writing memos after interviews, triangulation between nurse and patient participant results, peer debriefing, and nurse participant reviews of their transcripts.

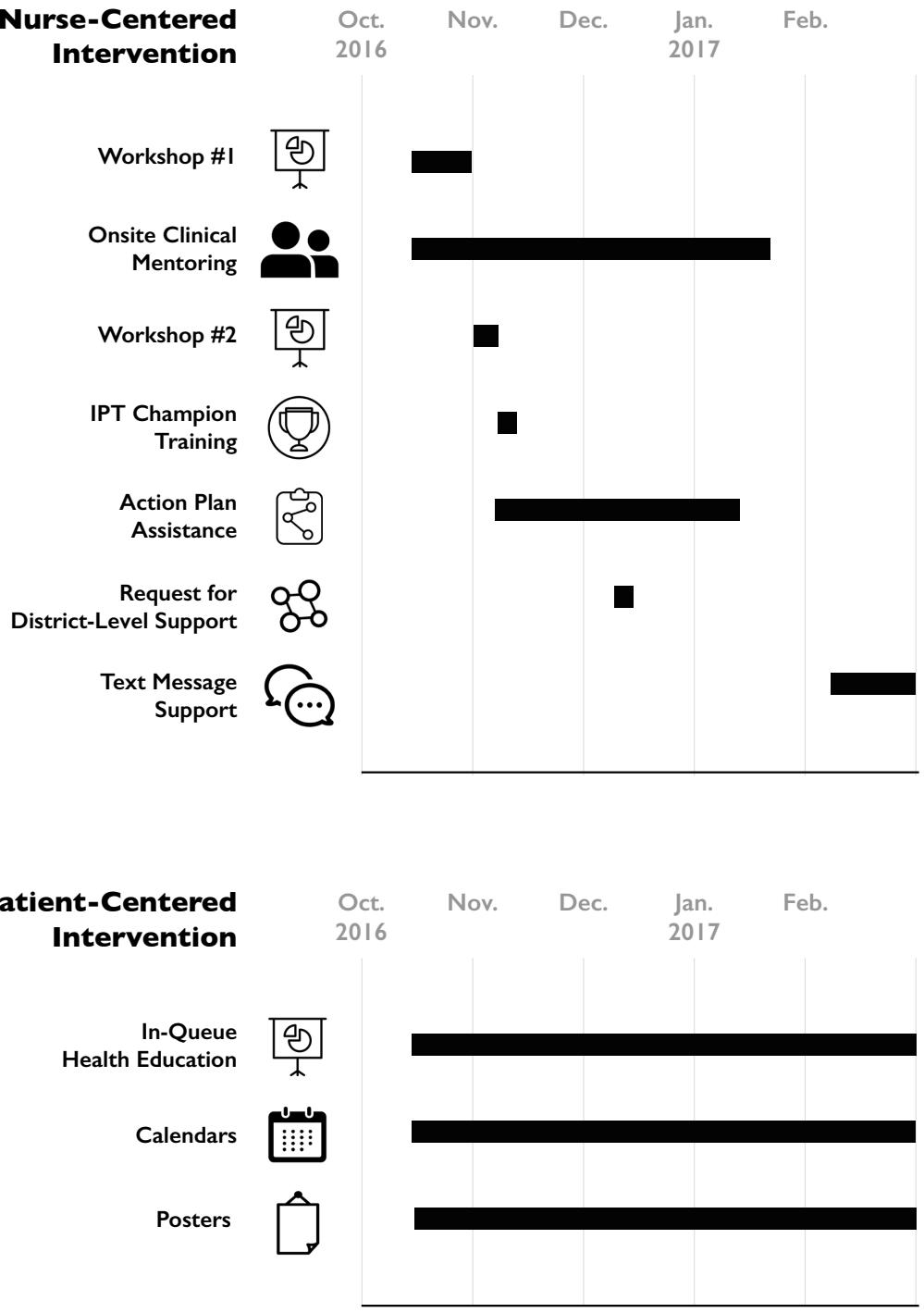
Conclusion

Tuberculosis remains the single greatest cause of death among people living with HIV. Preventive treatment for TB is a crucial element for elimination, especially as case detection rates stagnate. This study described the first documented interventions to improve the provision of IPT to HIV-positive adults in South Africa. We evaluated both nurse and patient perspectives on the immediate and medium-term impacts of the interventions. Although nurses and patients found the interventions acceptable, nurses still required extensive training to overcome the ambiguity of the national IPT guidelines and patient education was not sufficient to motivate change. Complicated guidelines without adequate oversight or improved patient-provider communication will hinder preventive treatment implementation. Future guidelines should provide comprehensive instructions to cover all potential patient and medication stockout scenarios, be written in simple language, and be communicated with visual diagrams like decision trees.

Taken together, this study and others show that implementation barriers for IPT in South Africa will continue to persist without changes in *both* patient-provider communication and district-level action to increase support and monitoring for IPT. More research is needed to evaluate the effectiveness and sustainability of multi-level interventions that concurrently educate nurses and patients on IPT, provide sustained support to nurses through text messaging and district-level monitoring, and promote patient-centered communication.

FIGURES

Figure 4.1 – Intervention timeline for the educational intervention among patients living with HIV and nurses in four clinics across Potchefstroom, South Africa from October 2016 to November 2017



TABLES

Table 4.1 – Components of the nurse-centered intervention led by a clinical mentor within two clinics in Potchefstroom, South Africa from October 2016 to November 2017

Component	**Study Week**	**Frequency (Average duration)**	**Total Hours** (%)	**Description**	**Theoretical Basis**
Leading Group Workshop #1: Education and Reflection	1-2	Once per clinic (90 minutes), including 1 hour and 15 minutes more for absent nurses	4.3 (4.5)	Led exercise to map individual procedures for HIV-patients; teach and role play national guidelines; brainstorm clinic-specific barriers	—
Mentoring	1-14	36 sessions with 11 nurses *(88 m)*	55.8 (58.8)	Modeled behavior to individual nurses and support patient interactions	Modeling target behaviors to promote self-efficacy through social learning, from Bandura's social cognitive theory [17], [28].WHO Guidelines for Clinical Mentoring for HIV Support in Resource Constrained Settings [10]
Leading Group Workshop #2: Action Plan	3	Once per clinic *(55m)*, including 1h 15m more for absent nurses	3.1 (3.3)	Brainstormed solutions to clinic-specific barriers and selected a few solutions to create an Action Plan	Results-based management, from the United Nations Development Group [31]; Theory of Change, from the Aspen Institute [32]
Training the IPT Champion	4	3 times *(31.7 m)*	1.6 (1.7)	Elected a nurse from the clinic, i.e. an "IPT Champion," to continue the Action Plan after the intervention ended	The Expert Recommendations for Implementing Change Project [30]
Assisting with the Action Plan	4-14	21 times (*71.2 m*)	24.9 (26.3)	Worked with operations manager, pharmacist, data capturer, and clerk to implement Action Plans	—
Communicating with the district coordinator	8	Once *(72 m)*	1.3 (1.3)	Explained barriers to subdistrict HIV/TB coordinator & requested additional support	—
Supporting nurses via text messaging	18-20	6 text messages sent; read within 19 minutes of receipt on average	4.0 (4.2)	Sent text messages	Cues to Action, from the Health Behavior Model [33]

Table 4.2 – Clinic-specific barriers to prescribing isoniazid preventive therapy (IPT) as listed by nurses during the first workshop of the nurse-centered interventions executed in two clinics across Potchefstroom, South Africa from October 2016 to November 2017

Barriers Shared by Both Clinics	
• No previous training on IPT guidelines • Not comfortable with IPT guidelines • Do not know how to read a tuberculin skin test (TST) • Unsure what prescription duration to give to patients • Stock outs of IPT, TST, and related medications (e.g. pyridoxine (vitamin B6) to reduce peripheral neuropathy) • Wanting to ensure that patients are on IPT for the right duration but lacking a dedicated IPT register or reliable paper medical record system to do so • Perceiving that patients are not ready for IPT • Alcohol use, which is prevalent in this community, is not advised while using IPT. Uncertainty whether patients will really stop drinking if instructed. • Screening, prescription, and patient education are too time consuming, given the lack of staff and knowledge	
Clinic A	**Clinic B**
• Not understanding the IPT guidelines • Not knowing about IPT • Not knowing how to administer a TST • Not wanting to waste TST, which is typically in short supply and reserved to test children who have been exposed to tuberculosis	• No previous training on contraindications for prescribing IPT • No printed copy of IPT guidelines available in the clinic • Forgetting about IPT because it is prescribed three months after antiretroviral therapy initiation rather than simultaneously • Believing that patients will not come back to have their TST read • Not trusting that other nurses are tracking each time they prescribe IPT to patients and over- or under-dosing patients based on incomplete information

Table 4.3 — Participant demographics within four clinics (A, B, C, and D) participating in an educational intervention for people living with HIV and nurses in Potchefstroom, South Africa from October 2016 to November 2017

Nurses

ID	Clinic	Years at Clinical Level	Role	Age
1	A	0.9	Community Service Nurse	25
2	A	11	Professional Nurse	42
6	A	0.5	Community Service Nurse	24
7	A	10	Professional Nurse	40
8	A	11	Professional Nurse	42
10	A	2	Professional Nurse	26
3	B	5	Professional Nurse	40
4	B	9	Nurse Manager	36
5	B	4	Professional Nurse	43
9	B	6	Professional Nurse	54

Patients

ID	Clinic	Years HIV-positive	Sex	Age
1	C	Not reported	Female	–
4	C	4.3	Female	25
5	C	9.6	Female	36
7	C	0.2	Female	39
10	C	4.1	Female	37
2	D	Not reported	Male	–
3	D	Not reported	Female	25
6	D	8.6	Male	57
8	D	1.1	Female	20
11	D	10.9	Male	40

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CHAPTER 5: CONCLUSION

Summary of key findings

The goal of this dissertation was to evaluate effective interventions to improve health services and to provide TPT for PLHIV in South Africa. I helped to design, execute, oversee, and evaluate three interventions. Specifically, our first aim was to deliver TB and routine HIV test results via mobile phone and improve retention-in-care for high-risk patients. Our second aim was to increase the number of people receiving LTBI tests and TPT. Our third aim was to explore the implementation outcomes of an education-based intervention to improve uptake of TPT among nurses and patients. Our findings contribute the following evidence to better implement the Three I's and reach the End TB goal to provide TPT to 90% of PLHIV by 2035:

1. More patients received their CD4, VL, and TB results within a week, when delivered via mobile phone versus needing to return to the clinic (73% versus 9%).
2. Patients who received their CD4, VL, or TB results via mobile phone were more likely to return, if instructed that their result was medically concerning, than the control group, who were all instructed to return for their results (20% versus 9%).
3. Although the majority (95%) of intervention patients believed that receiving their results via mobile phone in their native language was more private and confidential than picking up their results in-person, only a quarter read

the full message and even fewer called back to discuss their results with a nurse.

4. Clinics delivered an absolute 60% more LTBI tests and 12% more TPT prescriptions when they were randomized to integrate QGIT testing into routine HIV care, as compared to the standard-of-care; intervention clinics also delivered TPT more quickly to patients (29 vs 54 days). Despite improvements in the intervention arm, just under half (45%) of PLHIV received TPT, as compared to the End TB goal of 90%.
5. Nurses were accepting of a highly-tailored, education-based intervention about TB prevention and used their newfound tools to greatly increase prescriptions of TPT, however, their changes were not sustained over time due to factors outside their control, including: lack of district-level prioritization, support, and oversight; patients resisting treatment due to misunderstanding the difference between LTBI and TB disease; stock outs of TPT; and overwhelming work demands due to staff shortages.

Public health implications

These aims demonstrate that clinic-level interventions can effectively increase the number of high-risk patients who are retained in care and can persuade nurses to prescribe TPT. However, despite the interventions precipitating meaningful change as compared to the standard-of-care, none managed to persuade patients and nurses to fully adhere to national guidelines.

For example, in Aim 1, there was a 20% return rate among patients summoned via text message; in Aim 2, 45% of patients received TPT in the intervention arm. In Aim 3, there was an increase of TPT prescriptions from 1% to 7% in the nurse-focused intervention arm. Furthermore, the effectiveness of the interventions in Aims 2 and 3 waned over time, with the effect in Aim 3 being nullified after the study ended.

These findings indicate that our interventions alleviated some but not all barriers to quality health care. In Aim 1, a majority of patients who needed additional care did not return quickly to address their low CD4 counts, high viral loads, or positive TB results. Although we did not qualitatively interview patients in this aim, research in other parts of South Africa suggest that patients are often unable to skip work to seek care, were unable to make clinic hours, could not afford transport, were disincentivized by long wait times, and felt disrespected by staff [1–3]. In Aims 2 and 3, nurses increased their prescriptions of TPT to their patients with HIV but still missed more than half of eligible PLHIV. This may be in part due to patient-related barriers. For example, nurses in this and other studies reported that patients did not view TPT as necessary and attended clinic unreliably, which made nurses hesitant to prescribe antibiotics like TPT, which need to be taken consistently to prevent drug resistance [1,4,5]. Yet, patients in Aim 3 also reported that it was difficult to interact with nurses and ask questions because they were so rude and unapproachable. Barriers in this study mirrored others in South Africa — nurses from intervention clinics received additional

support from our study teams but were still plagued by high staff turnover; overwhelming patient-to-nurse ratios; quickly and ever-evolving national policies; supply shortages of TPT; and lack of overarching management support [4,6–8].

These structural impediments — including poverty, under-resourced public clinics, and interpersonal disharmony between nurses and patients — are all rooted in long histories of oppressive practices against Blacks in South Africa [9,10]. High rates of poverty among Black people can be traced back to economic disenfranchisement through land annexation and proletarianization [11]. Under-resourced public clinics are the result of years of investment into private clinics and exclusion of so-called “Black homelands” from national health services [12]. Interpersonal nurse-patient disharmony stems from years of missionary-led, moralistic-driven clinical practice that degrade patients, especially women, with HIV and have been embedded into nursing curriculums and culture [12,13].

Such structural impediments persisted after intensive, outside intervention at the clinic-level. To reach the 2025 End TB Goal of prescribing TPT to 90% of eligible PLHIV, this dissertation indicates there is a strong need for multi-level, comprehensive interventions that address historical, social determinants of health [14]. Furthermore, more research is required to extend the effect of the interventions in Aims 2 and 3; for example, using evidence-based strategies for sustainability like spaced repetitions of training materials to improve skills integration [15]. Indeed, some recent research employing multi-level

interventions has shown promise [16]. Though imperfect, these clinic-level interventions were moderately successful in preventing unnecessary clinic visits and promoting TPT; such interventions should be considered as potential options by policymakers.

Challenges and limitations

This dissertation confronted several methodological and inferential limitations. In Aim 1, we initially chose to implement the study as a pilot. As such, we enrolled patients to try the MatlaMobile intervention, and then later, when we discovered we had the resources for a comparison arm, we enrolled patients who did not receive the MatlaMobile intervention. Because this study was a nonrandomized trial with non-concurrently enrolled arms, it is susceptible to secular biases. In other words, the differences between groups may be partially due to the intervention and also partially due to changes in clinical practice during the two separate time periods. Two alternatives to improve comparability between groups would have been to (1) find an interchangeable cohort in the region that was enrolled and followed at the same time as the intervention arm and (2) using propensity scores or other similar methods.

We also conducted a satisfaction survey among patients who received the MatlaMobile intervention on their phones. The vast majority (≥ 90%) of participants responded positively to every question, which suggests a social desirability bias, in which interviewees respond untruthfully and instead attempt

to appease the interviewer [17]. One way to address this challenge would have been to include a comparison to patients in the comparison arm about their satisfaction with standard care. The satisfaction survey may also suffer from a recency bias since patients were comparing their recent use of the intervention with their prior experiences with standard care. Because of these social desirability and recency biases, the true level of patient satisfaction with the MatlaMobile intervention may be lower than reported here, however, there is an overall positive signal in this and other studies, which demonstrate relatively high acceptability of mHealth for HIV care [18,19].

In Aim 2, we used highly constrained cluster randomization to assign clinics to treatment arms. To attain greater balance between arms, we controlled on geographic quadrant, the number of people being screened and diagnosed with HIV, and the number of people being treated with ARTs. However, we did not control for type of clinic — primary health centers, community health centers, and gateways. Such clinics have different availabilities and types of care. For example, community health centers are have hours outside of the workday (i.e., nights and weekends) but provide a narrower spectrum of care than primary health centers. Gateway clinics are located near to hospitals and act as entry points for referrals. There were only two gateway clinics in our source population, and we randomly assigned both to the control arm. Due to the small number of clinics involved in the trial, this imbalance may have resulted in a larger number of people with advanced TB/HIV disease to be enrolled in the control arm.

However, an in-process multi-level analysis with these data demonstrate, nurses are more likely to prescribe TPT to PLHIV with low CD4 counts. As such, we would expect for this imbalance to increase the amount of TPT prescribed in the control arm and hence lessen the difference between the intervention and control arms (i.e., attenuate the effect of the intervention).

In Aim 3, during which we spoke with nurses and patients about another intervention to promote TPT, our qualitative interviews may have also been subject to bias. Our study staff, consisting of two lay counselors and a nurse mentor, worked full-time onsite alongside the clinic nurses at least four times weekly and reported mostly amicable relationships. Additionally, the nurse mentor was related to a well-known head nurse in a nearby city, and her surname was often recognized and respected. Because of the clinic nurses' familiarity with our study staff, those nurses may have fallen subject to some social desirability bias as well. Particularly, the nurses may have felt pressure to feign acceptance of the intervention even if they found it unpleasant or inappropriate. For example, clinic nurses may have believed that our qualitative researcher was evaluating the study staff and in turn, wanted to report on their performance favorably. If the clinic nurses had positive social connections with our study staff, then they may not have offered honest criticisms. Similarly, patients received printed calendars after each in-queue education session. Patients may have felt indebted to the study and described the educational sessions in a more positive light than they truly perceived. Despite this possibility,

the qualitative and quantitative evidence from this intervention are mutually reinforcing, and several nurses and patients offer criticism in their interviews. Both suggest that while social desirability may have somewhat influenced the clinic staff and patients, the qualitative interviewer was sufficiently skilled in persuading interviewees to share some of their criticisms of our intervention.

Implications and future directions

These findings are particularly relevant given new national policies in South Africa. The revised 2019 ART Clinical Guidelines indicate that PLHIV are no longer required to receive an LTBI test prior to TPT initiation and that pregnant PLHIV with a CD4 > 100 should not receive TPT until six weeks after delivery [20]. Later, in 2021, a systematic review of tuberculosis screening in ambulatory PLHIV suggested that all PLHIV should receive a Xpert regularly in addition to current screenings with the WHO4SS, which is a policy under consideration in South Africa [21,22]. Although these changes will likely simplify the treatment algorithm for TPT and bolster nurse confidence that patients do not have TB disease, they do not address other barriers to TPT described in this dissertation. As such, future work should explore whether these policies change nurses' knowledge, skills, and behaviors related to LTBI and TPT. In the future, policies in South Africa should focus on (1) encouraging knowledge about LTBI and patient-centered care in nursing school curricula, (2) improving policy rollouts through regular onsite training and clinical mentorship (3) addressing workforce

and TPT supply chain issues, (4) investing in clinical leadership to improve the stewardship and management of the health system, and (5) improving patient satisfaction of their healthcare experiences by offering routine test results and nurse care via mobile phone.

Conclusions

We designed three interventions to improve patient care for PLHIV in South Africa, We found evidence that these interventions increased retention-in-care for patients in need of medical attention and increased TPT for eligible PLHIV. The initial success of these interventions is promising and offers a model for national policies toward mobile delivery of routine HIV and TB results, integrated LTBI testing during CD4 blood draws, and tailored clinic mentorship. Despite the successes of these interventions, none sufficiently motivated complete adherence to national TB/HIV guidelines due to continued structural barriers such as patient impoverishment and underinvestment in public clinics. Further research on multi-level interventions is necessary to reach the End TB Goals of 2025.

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