THE IMPACT OF GUIDELINE CHANGES ON TIMING OF HIV DIAGNOSIS, ART UPTAKE, AND IPT PROVISION AMONG PEOPLE LIVING WITH HIV IN SOUTH AFRICA

by
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Abstract

Background

South Africa's National Department of Health adopted universal test and treat (UTT) for people living with HIV (PLHIV) in September 2016. We sought to describe the impact of this policy change on timing of HIV diagnosis, antiretroviral therapy (ART) uptake, and provision of isoniazid preventive therapy (IPT) among newly diagnosed PLHIV.

Methods

We included adult PLHIV without tuberculosis who were diagnosed at 14 clinics participating in a cluster randomized trial between January 2015-May 2017. We evaluated the impact of UTT on 30-day ART uptake using difference-in-differences to compare newly eligible PLHIV (CD4 ≥500 cells/mm^3) to always eligible PLHIV (CD4 ≤500 cells/mm^3). We used quantile (median) regression to estimate the change in median CD4 count at diagnosis and ART initiation before and after implementation of UTT and used Poisson regression to evaluate the association between CD4 count strata and ART initiation. We present IPT provision as simple proportions and evaluated predictors of IPT provision to participants who initiated ART using multi-level Poisson regression. All regression analyses incorporated cluster-robust standard errors.

Results

Removal of the CD4-based eligibility threshold resulted in a 47% (95% CI: 35%, 59%) increase in 30-day ART uptake among newly eligible participants. The median (IQR) baseline CD4 count was 315.5 (168.0-496.0) cells/mm^3, with no

change observed before and after UTT. After adjustment, a clinically meaningful increase in CD4 count was observed at ART initiation (92.9 cells/mm^3; 95% CI: 54.0, 131.8). Compared to patients with CD4 counts between 51-200 cells/mm^3, patients diagnosed with CD4 counts between 351-500 cells/mm^3 were less likely to initiate ART under pre-UTT (aRR: 0.79; 95% CI: 0.64, 0.97) while no association was observed under UTT. Of 1,184 PLHIV enrolled at standard of care sites, 24% started IPT. Among participants who started ART ≤30 days, pregnant women (PR: 0.67; 95% CI: 0.49, 0.94) were less likely to be prescribed IPT than non-pregnant women.

Conclusions

Removal of the ART-eligibility threshold resulted in a large increase in ART uptake, with similar initiation rates across all CD4 strata. However, ART and IPT initiation are below target levels and interventions to improve uptake will likely be required.

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Chapter I: Introduction and background

HIV globally and in South Africa

In 2017, approximately 36.9 million people were living with human immunodeficiency virus (HIV) globally.[1] With improvements in antiretroviral therapy (ART) coverage, HIV-related deaths have declined by more than 50% since 2007 and the number of new infections has declined by 16% since 2010.[1,2] Despite these gains, HIV remained among the top twenty leading causes of death worldwide in 2016 and was the second leading cause of death in the World Health Organization (WHO) African region in that year.[3]

The UNAIDS 90-90-90 goals state that in order to end the HIV/AIDS epidemic by 2030, 90% of all people living with HIV (PLHIV) must be diagnosed, 90% of those diagnosed must be on ART, and 90% of those on ART must be virologically suppressed by 2020.[4] According to estimates from 2017, 75% of PLHIV globally are diagnosed, 79% of those who are diagnosed are on ART, and 81% of those on ART are virologically suppressed.[1]

South Africa has the world's largest population of people living with HIV (PLHIV), estimated at 7.39 million individuals in mid-2018 by the South Africa-specific Thembisa model.[5] HIV prevalence is estimated at 18.9% among individuals ages 15-49 and the majority of transmission occurs through heterosexual sexual intercourse.[5,6] Estimates of HIV prevalence among the 15-49 year-old age group are highly variable provincially, ranging from 10.3% in the Western Cape to 27.4% in KwaZulu-Natal.[7] HIV prevalence is higher for women (24.4%) than men (13.5%) and prevalence increases in women at an earlier age than men.[5,8] According to South Africa's Human Sciences Research Council,

approximately 5-6% of men and women ages 15-19 were estimated to be HIV-infected in 2017, increasing to 16% of women ages 20-24 compared to 5% of men and HIV prevalence was higher for adult women of all ages.[8] Research to understand the divergence in HIV prevalence among young adults has suggested that age-disparate relationships may be a contributing factor.[9,10]

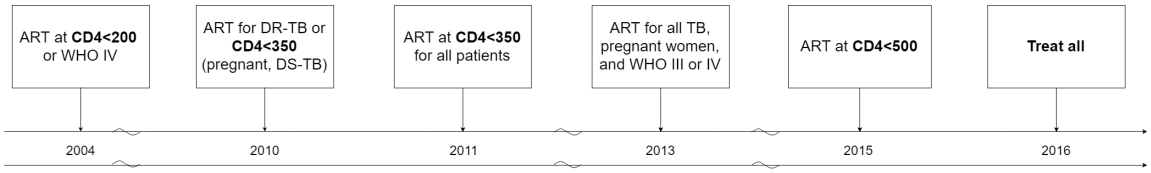
South Africa has made substantial progress towards achieving the UNAIDS 90-90-90 goals. In mid-2018, it was estimated that 90.5% of PLHIV have been diagnosed and 88.4% of those on ART were virologically suppressed at a threshold of <1,000 copies/mL.[5] However, ART coverage among those who have been diagnosed was just 68.4%.[5] Wide variability at the provincial level was also observed for this target with a range of 58% of diagnosed PLHIV on ART in North West province to 83% in the Northern Cape.[7] Thus, despite the progress that has been made towards the first and third 90s, the low levels of ART uptake have left South Africa in a vulnerable position for epidemic control. Combining the 90-90-90 targets results in an overall goal of 73% of PLHIV diagnosed, on treatment, and virologically suppressed. The most recent estimate for South Africa is at 54.7% nationally, with estimates ranging from 45% to 64% provincially.[5,7]

When to start ART and South Africa's HIV treatment guidelines

HIV diagnosis and treatment are provided free of charge in public-sector facilities in South Africa and the public-sector provides more than 90% of HIV care to South African PLHIV.[11] Public-sector provision of ART began in South Africa in 2004. At the time, treatment was available to PLHIV with CD4 counts

<200 cells/mm^3 or a WHO Stage IV defining illness.[12] Guidelines were updated over time to reflect growing scientific evidence in support of earlier treatment initiation (Figure 1.1).

Figure 1.1. Timeline of changes to the South African NDoH HIV treatment guidelines



Observational data provided mixed results regarding the benefit of earlier treatment initiation. An analysis of over 20,000 PLHIV enrolled across 18 cohort studies in North America and Europe published in 2009, observed an increased risk of AIDS or death for delayed ART initiation at CD4 counts between 251-350 cells/mm^3 compared to initiating between a CD4 count of 351-450 cells/mm^3.[13] No benefit to earlier ART initiation was observed at higher CD4 counts.[13]

Results from clinical trials were more definitive. A randomized trial conducted in Haiti observed a 4 times increased hazard of mortality with ART initiation at CD4 counts <200 cells/mm^3 vs between 200 and 350 cells/mm^3. There was also a doubling in the hazard of incident tuberculosis (TB) with ART initiation at lower CD4 counts.[14] Five years after the results of the Haiti trial, two studies, START and TEMPRANO, were published simultaneously in the New England Journal of Medicine. The START trial randomized asymptomatic PLHIV with CD4 counts >500 cells/mm^3 to immediate or deferred ART initiation and observed a 72% reduction in the hazard of a serious AIDS-related event (including death).[15] TEMPRANO, which used a 2x2 factorial design, randomized

patients with a CD4 count <800 cells/mm^3 to a combination of early vs standard timing of ART initiation and 6 months or no isoniazid preventive therapy (IPT). The results showed a 44% reduction in the hazard of mortality or serious illness, including among patients with a CD4 count ≥500 cells/mm^3.[16] In addition to improved survival and reductions in the incidence of severe illnesses conferred by earlier ART initiation, a public health benefit was also shown in the results of HPTN 052. HIV-serodiscordant couples in which the HIV-positive partner had a CD4 count between 350 to 550 cells/mm^3 were randomized to immediate versus delayed (CD4 <250 cells/mm^3 or an AIDS-defining illness) ART.[17] The results demonstrated a 96% reduction in the hazard of transmission from an HIV-positive to HIV-negative partner with earlier ART initiation.[17]

In response to the strong evidence generated for both individual and public health benefits of earlier ART initiation, the WHO updated their HIV treatment recommendations to a CD4-eligibility threshold of 350 cells/mm^3 in 2010,[18] 500 cells/mm^3 in 2013,[19] and recommended a universal test and treat strategy in 2015.[20] South Africa closely followed the WHO recommendations, raising the eligibility threshold to 350 cells/mm^3 in 2011,[21] to 500 cells/mm^3 in 2015,[22] and adopted universal test and treat in 2016.[23]

CD4 counts over time and ART uptake

Despite increases in ART coverage in South Africa through progressive expansions of ART eligibility criteria, HIV was the second leading natural cause of death among 15-44 year-olds in 2016, accounting for approximately 10.5% of deaths.[24] While CD4 counts at presentation to HIV care have increased over

time, a substantial proportion of patients still present late, contributing to HIV-related morbidity and mortality. Of all CD4 counts conducted in 2017 in the Western Cape, approximately 20% were ≤200 cells/mm^3.[25] Among the 5% of PLHIV with CD4 counts that were ≤50 cells/mm^3, 27% were newly diagnosed.[25] At the national level, 33% of PLHIV presenting for care in 2016 had a first CD4 count <200 cells/mm^3.[26] While this is a substantial decline from the 47% that presented with a CD4 <200 cells/mm^3 in 2005,[26] it indicates that a large proportion of PLHIV have not benefitted from ART-eligibility expansions. This is especially true for men who were approximately 60% more likely than women to present to care with a CD4 count <200 cells/mm^3 in 2016.[26]

While more and more PLHIV are presenting earlier in the course of infection, previous research has raised concerns that asymptomatic patients may be less likely to initiate ART than their sicker peers. Several qualitative studies among both PLHIV and health care providers have noted feeling healthy as a reason for ART refusal, as patients associated the need for ART with physical symptoms.[27–31] Quantitative studies from KwaZulu-Natal have also noted an association between CD4 count and ART initiation. In a study of more than 4,500 PLHIV who presented for care between 2011 and 2012 with an ART-eligible CD4 count, 67% of patients with a CD4 count ≤50 cells/mm^3 initiated ART within 6 months.[32] ART initiation declined as CD4 counts increased. Of the PLHIV who presented with a CD4 count between 151-200 cells/mm^3, 59% initiated ART within 6 months, dropping further to 48% among PLHIV with a CD4 count between 301-350 cells/mm^3.[32] Likewise, in a study of over 24,000 patients with

ART-eligible CD4 counts between 2007 and 2013, 74% of PLHIV with a CD4 count between 101-200 cells/mm^3 initiated ART compared to 53% of PLHIV with a CD4 count >200 cells/mm^3.[33]

Failure to initiate PLHIV with higher CD4 counts on ART has raised concerns that the impact of a treat all strategy will be muted. A modeling study based on data from KwaZulu-Natal estimated that only 27% of PLHIV diagnosed with a CD4 count >500 cells/mm^3 would initiate ART in a treat all scenario.[34] As some of those individuals would have initiated even under pre-treat all guidelines (due to pregnancy, TB, or another WHO Stage III/IV defining illness), just 19% would initiate due to the removal of the treatment eligibility threshold.[34] However, early results from Rwanda in the treat all era indicate that these concerns may be unfounded. Overall, the proportion of PLHIV who initiated ART within 30 days of enrollment increased from 47% in the pre-treat all period to 78% in the treat all period.[35] Among PLHIV with a CD4 count >500 cells/mm^3, 36% initiated ART within 30 days in the pre-treat all period compared to between 50%-60% at other CD4 count strata.[35] In the treat all period, an estimated 88% of PLHIV with a CD4 count >500 cells/mm^3 initiated compared to 70%-90% of other CD4 count strata.[35] Likewise in a study of 6 countries in East and Southern Africa, 59% of PLHIV initiated ART within 30 days of enrollment under the pre-treat all guidelines compared to 82% under treat all guidelines.[36] In the treat all era, little difference in ART initiation was observed by CD4 count category.[36] The impact of the removal of the CD4-based ART eligibility threshold has yet to evaluated in South Africa.

TB globally and in South Africa

TB is the leading infectious cause of death worldwide.[37] In 2017, approximately 10 million people had active TB disease with the vast majority (87%) occurring in 30 high burden countries, including South Africa.[37] Most (85%) TB is pulmonary, though TB can occur anywhere in the body, and is spread through the air when a person with active TB disease coughs.[38] Active TB disease can occur from recent infection or through reactivation of a latent infection. While it is estimated that approximately one-quarter of the world (1.7 billion people in 2014) is infected with latent TB,[39] most will never progress to active disease. Once infected, the strongest risk factor for active TB disease is HIV, estimated at a 20-40 fold increased risk compared to people without HIV.[38] Other risk factors include diabetes, smoking and alcohol use, exposure to indoor air pollution, and silicosis, among others.[38] In a meta-analysis which included 11 studies of PLHIV, ART was shown to reduce the risk of TB in PLHIV by 65% across all CD4 count categories, with greater protection at lower CD4 counts (two studies; HR for CD4 <200 cells/mm^3: 0.16; 95% CI: 0.07, 0.36).[40] However, despite the substantial reduction in risk, PLHIV on ART still have an incidence rate of TB five times that of their HIV-negative counterparts.[38]

In addition to having the world's largest population of PLHIV, South Africa has the world's second highest incidence rate of TB, estimated at 567 cases per 100,000 individuals in 2017.[37] TB is the leading natural cause of death among adults ages 15 to 64, accounting for 8.0% (45-64 year-olds) to 11.2% (15-44 year-olds) of deaths in 2016. While HIV is the biggest driver of TB incidence in

South Africa, TB is known to be a disease of poverty and thrives in areas of over-crowding,[41] making South Africa's urban townships hotspots for TB transmission. The burden of latent TB infection (LTBI) in these communities is substantially higher than global estimates. In townships of Johannesburg and Cape Town, the prevalence of LTBI has been estimated at 34% to 45%, respectively, with increasing prevalence observed with increasing age.[42,43] Peak LTBI prevalence was observed among HIV-negative 31-35 year-olds in Cape Town, estimated at 88%.[43]

Latent TB infection and isoniazid preventive therapy

LTBI is typically diagnosed using a tuberculin skin test (TST) in resource-limited settings, including South Africa. To perform a TST, purified protein derivative (PPD) is injected under the skin of the forearm and the test should be read 48-72 hours after placement.[44] An induration of at least 5 mm is considered positive in PLHIV.[44] Latent TB infection can be treated using TB preventive therapy (TPT). TPT is a pillar of the WHO's End TB strategy which calls for a 95% reduction in the number of TB-related deaths and a 90% reduction in the incidence rate of TB by 2035 (compared to 2015 levels).[45] Current WHO guidelines consist of four TPT regimen options: isoniazid daily for at least 6 months, rifampicin plus isoniazid daily for 3 months, rifapentine and isoniazid weekly for 3 months, or rifampicin daily for 3-4 months.[46] TPT is also an important component of South Africa's National Strategic Plan for HIV, TB, and STIs (NSP) which includes a goal to have >90% of PLHIV on ART started on TPT by 2021.[47] The 2015 South African guidelines recommend isoniazid, more

commonly called isoniazid preventive therapy (IPT), and targets PLHIV, including pregnant and breastfeeding women, and HIV-negative children <5 years-old who are contacts of a TB case.[22] For children <5 years, 6 months of IPT is recommended while varying durations of IPT are recommended for adult PLHIV, dependent on TST and ART status (Table 1.1).[22]

Table 1.1 IPT guidelines according to TST and ART status as per 2015 South African National Department of Health guidelines for treatment of HIV infection

	PLHIV not yet on ART	PLHIV on ART
TST positive	36 months[1]	36 months
TST negative	No IPT[2]	12 months[2]
TST not available	6 months[2]	12 months[2]

[1]IPT should be stopped if TST later becomes negative
[2]If later TST becomes positive, IPT should be extended to 36 months

IPT has been demonstrated to be effective in reducing the risk of active TB disease in PLHIV, even among those on ART. In a meta-analysis of randomized controlled trials, IPT use was associated with a 35% reduction in the risk of TB (RR: 0.65; 95% CI: 0.51, 0.84) with stronger associations for TST-positive PLHIV.[48] Studies conducted in Southern Africa have found similar results. In a randomized trial of PLHIV on or starting ART in Cape Town, 12 months of IPT use was associated with a 37% reduction in the risk of TB (HR: 0.63; 95% CI: 0.41, 0.94) compared to placebo with the greatest reductions observed in the first year (HR: 0.52; 95% CI: 0.41, 0.94).[49] In a trial of PLHIV in Botswana, 36 months of IPT was associated with a 74% reduction in the risk of TB compared to 6 months of IPT in participants with a positive TST (HR: 0.26; 95% CI: 0.09, 0.80), though little to no benefit was observed for those with a

negative TST (HR: 0.75; 95% CI: 0.38, 1.46). This study also demonstrated an additive effect of ART combined with IPT for TST-positive PLHIV. Compared to participants who received 6 months of IPT with no ART, those who received 360 days of ART and 36 months of IPT had a 96% reduction in the risk of TB (HR: 0.04; 95% CI: 0.005, 0.35).[50]

While the benefits of IPT are clear, concerns have been raised that the durability of protection wanes quickly after cessation of IPT use in high-burden settings. In the Botswana trial, the authors noted that the incidence of TB increased approximately 6-7 months after completion of treatment in the 6 month group.[50] Likewise, in a study that assessed the impact of 9 months of IPT among gold miners in South Africa, the rate of TB was reduced by more than half among participants participating in intervention vs control mines (adjusted rate ratio [aRR] for the first 9 months: 0.42; 95% CI: 0.20, 0.88). However, the protective effect was lost almost immediately after completion of treatment (aRR 9-18 months: 0.93; 95% CI: 0.53, 1.61).[51] The lack of a long-term protective effect is likely in part a result of the high rate of TB transmission in these settings.

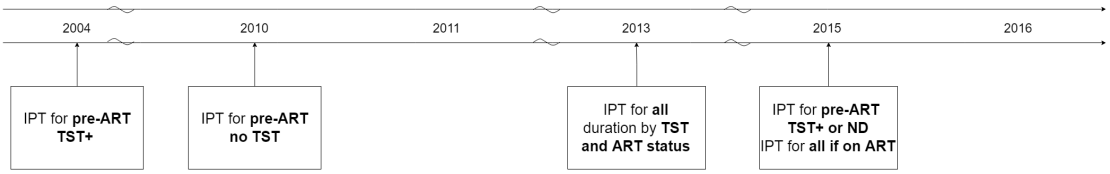
IPT use in South Africa and barriers to implementation

South Africa currently accounts for 39% of global IPT use.[37] Despite this, national reporting indicated that just 53% of PLHIV who were newly engaged in care started IPT in 2017. Previous research, however, has indicated that actual IPT provision may be even lower than stated reports.[52] In a study of three public-sector health facilities in Johannesburg that evaluated the impact of an intervention to improve IPT provision in 2015 to 2016, IPT provision prior to the

intervention at the three sites was <1%, 6%, and 34%.[53] Likewise, in a study of community-based HIV testing and linkage to care in KwaZulu-Natal conducted between 2013 and 2015, just 18% of participants who linked to a healthcare facility started IPT.[54] While isoniazid stock-outs have been reported by facilities in multiple provinces,[55] coverage of IPT at the facility level has generally been reported to be high. In a study of 49 randomly selected facilities across South Africa in 2011, 71% reported providing IPT.[56] However, even where available, IPT provision to eligible patients was still only 46%.[56]

There are a number of reasons why IPT provision remains below target levels. IPT guidelines have been updated alongside HIV guidelines since 2004, and have alternated TST requirements, target populations (i.e., pre-ART only vs all PLHIV), and IPT duration which may have induced confusion among healthcare providers (Figure 1.2). In a study of PEPFAR supported sites, IPT uptake in the three months prior to the initial removal of the TST requirement in 2010 showed that just 1.0% of patients started IPT.[57] This increased to 10.5% 12 months later,[57] after the TST requirement had been removed, indicating that TST may have been a barrier to IPT provision. In addition, with the requirement for TST re-introduced in 2013, global[58,59] and local[55] shortages of PPD for TST may also be a barrier. Guidelines in place during the period of analysis for this dissertation did allow for IPT initiation without a TST; however, the guidelines stated that TST must be done within one month of IPT start.[22]

Figure 1.2. Timeline of changes to the South African NDoH IPT guidelines



Qualitative research among healthcare providers and patients have also indicated that lack of patient and provider knowledge of IPT benefits, fears of inducing INH resistance, and the need to rule out active TB disease prior to IPT initiation are barriers to IPT provision.[53,60] The South African National Institute for Communicable Diseases TB drug-resistance survey noted that INH mono-resistance increased in new TB cases from 2.6% in the 2001-2002 survey to 4.5% in the 2012-2014 survey.[61] However, there is limited evidence to indicate that IPT is the driver of this increase. In a meta-analysis of 13 studies of the association between IPT use and INH resistance published in 2006, the risk ratio for resistance was 1.45 (95% CI: 0.85, 2.47).[62]

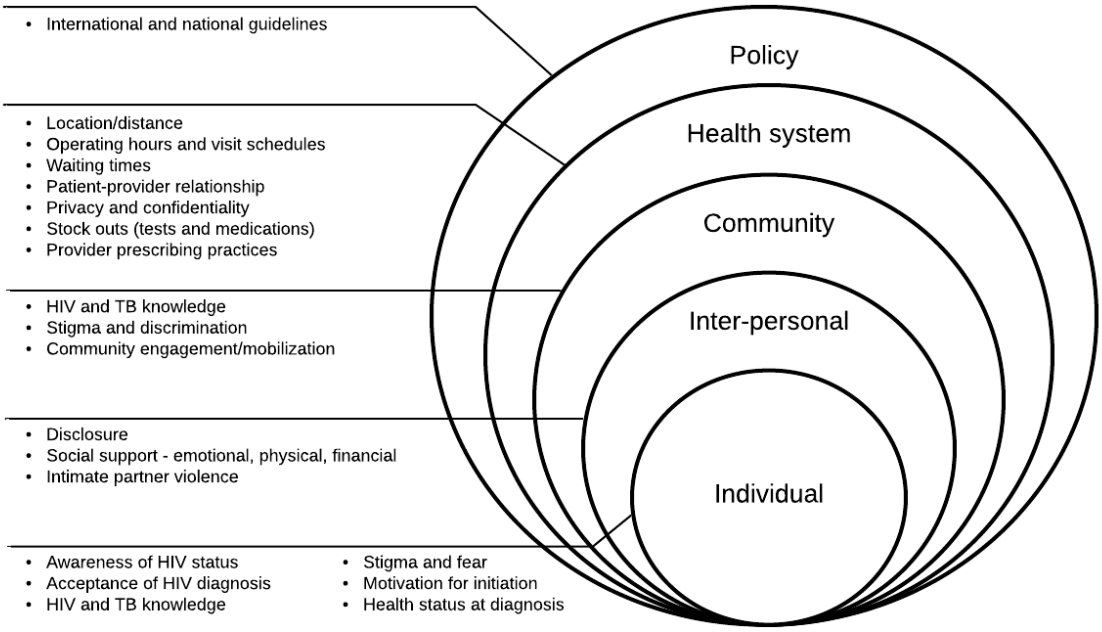
Conceptual framework

We used the social-ecological model informed by findings from the literature[27,29,31,53,60,63–66] to aid in conceptualizing our understanding of ART and IPT uptake (Figure 1.3). This model posits that there are factors at the individual, inter-personal, community, health system, and policy levels that influence a health behavior; in the case of this dissertation, ART and IPT initiation. In **aim 1**, we sought to focus primarily on the policy level to answer the questions: what is the impact of the implementation of the treat all guidelines on 30-day ART initiation in South Africa? Were there differential impacts by age or sex? In **aim 2**,

we focused on both the individual and policy levels to gain insight into whether there has been any change in timing of HIV diagnosis or health status at ART initiation (using CD4 count as a proxy measure for both) before and after implementation of the treat all guidelines. We also sought to answer the question, are PLHIV who are diagnosed with higher CD4 counts less likely to initiate ART than their sicker peers? Does this differ before and after the implementation of the treat all guidelines? Finally, in **aim 3**, we focused primarily on the health system and policy levels to understand whether increasing uptake of ART with the implementation of the treat all guidelines had a knock-on effect on IPT provision. We also described clinic-level variability in IPT prescribing practices and sought to answer the question, are health care providers targeting specific patients starting ART for IPT?

To answer these questions, we used data from a cluster-randomized trial conducted in 14 sites in North West province South Africa that enrolled more than 3,000 newly diagnosed PLHIV over a 2.5-year period. The objective of the trial was to compare an interferon-γ release assay, a laboratory-based blood test for the diagnosis of LTBI, to the TST for LTBI diagnosis and to determine if a laboratory-based test could increase IPT uptake.

Figure 1.3. Conceptual framework for ART and IPT initiation



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Chapter II: The impact of eliminating the CD4-based HIV treatment eligibility threshold on uptake of antiretroviral therapy in South Africa

Abstract

Background: Early initiation of antiretroviral therapy (ART) reduces morbidity and mortality in people living with HIV (PLHIV) and prevents transmission to uninfected partners. Thus, we sought to evaluate the impact of South Africa's universal test and treat (UTT) policy on 30-day ART uptake among newly diagnosed PLHIV.

Methods: Adult (≥18), non-pregnant PLHIV without tuberculosis who were newly diagnosed at 14 clinics in North West province between January 2015-May 2017 were included. We used difference-in-differences to estimate the effect of removal of the treatment eligibility threshold on 30-day ART uptake for newly eligible (CD4 >500 cells/mm^3) vs always eligible (CD4 ≤500 cells/mm^3) PLHIV. Results are presented as risk differences with 95% confidence intervals (CI). All regression analyses accounted for clustering by clinic using cluster-robust standard errors.

Results: Among 2,271 participants with a baseline CD4 count, 556 (24%) presented with a CD4 count >500 cells/mm^3. A small increase in 30-day ART initiation was observed for always eligible PLHIV in the UTT era compared to the pre-UTT era (58.6% vs 51.5%) while there was a large increase (61.1% vs 6.9%) for those newly eligible. Removal of the CD4 eligibility threshold resulted in an adjusted 46.7% (95% CI: 34.7%, 58.6%) increase in 30-day ART uptake for PLHIV with CD4 >500 cells/mm^3.

Conclusions: Removal of the CD4 eligibility threshold resulted in a large increase in ART initiation among newly eligible PLHIV. However, at 30 days only

60% of participants had initiated ART in the treat all era and additional interventions are required to increase initiation at all CD4 counts.

Introduction

Results from clinical trials and observational studies have provided definitive evidence that antiretroviral therapy (ART) for the treatment of HIV infection reduces morbidity and mortality among people living with HIV (PLHIV),[1–5] regardless of the stage of their infection at treatment initiation, and prevents further transmission.[6–8] On the basis of these findings, international guidelines have evolved in recent years to reflect the need for earlier ART initiation. In 2013 the World Health Organization (WHO) raised the recommended CD4 count eligibility threshold for non-pregnant adults and adolescents without active tuberculosis (TB) disease from ≤350 cells/mm^3 to ≤500 cells/mm^3.[9] The CD4 eligibility threshold was then eliminated in late 2015, ushering the world into the "treat all" era.[10] By mid-2018, 100% of the 35 high HIV-incidence countries that account for over 90% of new infections and 84% of all low- and middle-income countries had adopted a treat all policy.[11]

With an estimated 7.4 million PLHIV, South Africa is home to the world's largest population of PLHIV, and the National Department of Health (NDoH) supports the world's largest ART program.[12,13] In response to changing global recommendations, the NDoH adopted a CD4 eligibility threshold of ≤500 cells/mm^3 in January 2015, moved to a treat all approach in September 2016, and recommended same day initiation in September 2017.[14–16]

Analyses of routine data from 22 countries worldwide and South Africa have found that ART eligibility expansions increase overall ART uptake and do not result in negative impacts on ART initiation among those previously eligible

for treatment.[17,18] However, a modeling exercise based on data from KwaZulu-Natal estimated that removal of the treatment eligibility threshold would result in an increase in ART initiation of just 19% for individuals diagnosed with CD4 counts >500 cells/mm^3,[19] which may limit the impact of the treat all policy in South Africa. There is limited evidence, however, of the impact of the complete removal of the CD4 eligibility threshold in routine care in South Africa. Thus, in this analysis we sought to evaluate the effect of the removal of the CD4-based treatment eligibility threshold on 30-day ART uptake among newly diagnosed PLHIV with CD4 counts >500 cells/mm^3 compared to those with CD4 ≤500 cells/mm^3. As a secondary objective, we also evaluated whether there were differential impacts by sex and age.

Methods

Study sites

The data for this analysis were collected as part of a cluster randomized trial, TEKO. The TEKO trial was designed to evaluate the use of an interferon-γ release assay against the tuberculin skin test for diagnosing latent tuberculosis infection (LTBI) for isoniazid preventive therapy (IPT) eligibility in newly HIV-diagnosed adults (≥18). Participants were recruited from 14 public-sector healthcare facilities between November 2014 and May 2017.

The 14 study sites were located in the Klerksdorp and Potchefstroom communities of the Dr Kenneth Kaunda District in North West province which has an estimated HIV prevalence of 12.9%.[20] HIV treatment is provided in these sites

according to guidelines laid out by the South African NDoH. During the period of analysis, which covered patients enrolled between January 2015 to May 2017, HIV treatment was initially offered to all PLHIV with CD4 ≤500 cells/mm^3, those with WHO Stage 3 or 4 disease regardless of CD4 count, those with active TB disease, pregnant or breastfeeding women, and those with hepatitis B co-infection.[14] Guidelines recommended that patients initiate treatment within two weeks of receiving a CD4 count result with faster initiation (≤7 days) for those patients with a CD4 count <200 cells/mm^3 or WHO Stage 4 disease and immediate treatment initiation for pregnant women. Starting September 2016, restrictions on treatment provision on the basis of CD4 cell count were removed, and all PLHIV became eligible to receive treatment in public-sector facilities.[15]

Study population

Patients were eligible for inclusion in TEKO if they were diagnosed with HIV within 30 days of study enrollment. As the trial was focused on the diagnosis of latent TB infection, patients with active TB disease at the time of screening were excluded. Likewise, patients with contraindications for IPT, including excessive alcohol use or symptoms of peripheral neuropathy, were deemed ineligible for enrollment during the screening process. For this analysis, we included all study participants who enrolled in and met the eligibility criteria of TEKO between January 2015 and May 2017. Participants for whom evidence of prior knowledge of HIV status was later found (for example, evidence of clinic visits, CD4 counts, or viral loads recorded more than 30 days prior to study enrollment) and those for whom a baseline viral load (defined as prior to or within

7 days of study enrollment or prior to or within 7 days of ART initiation) was suppressed (<400 copies/mL) or undetectable were excluded as not being newly diagnosed (n=331). Patients later determined to have active TB disease at the time of HIV diagnosis were also excluded (n=64), as were those without an age recorded (n=5), those for whom no evidence could be identified that their files were ever attempted to be found (n=30), and those for whom the ART start date was prior to the earliest of study enrollment or the first CD4 count date (n=18). As pregnant women tend to have higher CD4 counts at HIV diagnosis, were offered immediate ART initiation throughout the study period, and likely have specific motivations for starting and adhering to treatment, they were excluded from regression analyses. Thus, all associations presented are for non-pregnant women and men. Women for whom pregnancy status was unknown or missing (n=89; 4.4% of women) were assumed to not be pregnant.

Eligible patients participated in a baseline interview at the time of study enrollment. During the interview, data was collected on indicators such as sex, pregnancy status, education level and employment status, income levels, household size, distance from the clinic and type of transportation used, and alcohol and tobacco use. After the initial interview, participants in the intervention arm provided blood samples for LTBI testing, with no further study-specific visits. Participants were then followed through their routine clinic files. We searched for study participants' medical records in paper files, South Africa's electronic HIV register, Tier.Net, and the South African National Health Laboratory Service's (NHLS) laboratory information system, TrakCare. Data abstracted from clinical

records included the ART initiation date, CD4 count, and viral load results. Data were collected using REDCap (Research Electronic Data Capture) hosted at Johns Hopkins University.[21]

Variable definitions

The primary outcome of interest was ART initiation within 30 days of HIV diagnosis, defined as the earliest of study enrollment or the first CD4 count date ("first known date"). Patients were categorized into either the pre-UTT or UTT cohorts based on their first known date. Those whose first known date was between January 2015 and June 2016 were categorized as the pre-UTT cohort and those whose first known date was between September 2016 and May 2017 were categorized as the UTT cohort. From July to August 2016, a break in enrollment occurred to allow for re-training of clinic staff on TEKO study procedures, including the use of the interferon-γ release assay and interpretation of its results. The exposure of interest was CD4 count at HIV diagnosis, defined as the first CD4 count recorded between 30 days prior to 30 days after study enrollment, and was categorized as >500 cells/mm^3 or ≤500 cells/mm^3. As patient files are often not created for individuals who do not return to the facility after testing HIV positive, patients for whom a file could not be found were assumed to not have initiated ART.

Confounders were chosen *a priori* as potential risk factors for failure to initiate ART and included sex and age (18-24, 25-34, 35-44, ≥45) as well as indicators of health status at HIV diagnosis (past TB diagnosis [yes/no], smoking status [never or former vs current], and alcohol use [yes/no]). We also included

indicators of socioeconomic status, including education level (grade 0-5 or less, grade 6-11, grade 12 or higher), employment status (employed vs unemployed), total family income per month (<1,000 ZAR, 1,000-5,000 ZAR, and >5,000 ZAR), and household size (1 person, 2 people, 3-5 people, ≥6 people), and indicators of distance from the clinic, including transportation type (on foot vs minibus taxi or other form of transportation) and travel time (≤15 minutes, 16-30 minutes, >30 minutes).

Statistical analysis

For the primary analysis, we sought to evaluate the impact of the introduction of the universal test and treat (UTT) guidelines on ART uptake among patients with CD4 counts >500 cells/mm^3 at diagnosis compared to those with CD4 counts ≤500 cells/mm^3. We used linear regression to estimate risk differences and 95% confidence intervals (CI) of 30-day ART initiation before and after the implementation of the UTT guidelines for each CD4 count stratum. We then used a difference-in-differences approach, which utilizes an interaction term with time (i.e., pre-UTT or UTT) and exposure (CD4 count stratum), to quantify the impact of the change in guidelines.

For the secondary analysis, we evaluated the impact of the implementation of the UTT guidelines stratified by sex and age categories (as previously defined), with a specific interest in the impact of UTT among those always eligible for ART (i.e., those with CD4 <500 cells/mm^3 at diagnosis). Risk differences and 95% CI of 30-day ART initiation comparing the UTT to pre-UTT cohorts are presented as well as the difference-in-differences results. All

regression results for both the primary and secondary analyses accounted for clustering by clinic using cluster robust standard errors. Unadjusted results utilize all available data while adjusted results are complete case analyses.

Ethical approval

Ethical approval was obtained from the Institutional Review Board of the Johns Hopkins University School of Medicine and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Results

Between January 2015 and May 2017, 2,965 individuals were newly diagnosed with HIV and enrolled in the parent cluster randomized trial. Of all participants, 20% (n=600) were women diagnosed during pregnancy, 86% of whom initiated ART within 30 days, with no differences observed by guidelines under which they were diagnosed. All pregnant women were excluded from further analyses, leaving 2,365 individuals included: 947 (40%) men and 1418 (60%) women. The median (interquartile range [IQR]) age at HIV diagnosis was 33 (27-41) years, the median (IQR) CD4 count was 314 (168-494) cells/mm^3, and 10% reported a previous TB diagnosis (Table 2.1).

Individuals diagnosed under the pre-UTT guidelines were similar to those diagnosed under the UTT guidelines. Just under 25% of individuals across both groups were diagnosed with a CD4 count >500 cells/mm^3. PLHIV with CD4 counts >500 cells/mm^3 were slightly younger in both cohorts (median [IQR]: 31 [25-39.5] and 30 [24-38.5] for pre-UTT and UTT cohorts, respectively) compared

to those with CD4 counts ≤500 cells/mm^3 (pre-UTT: 34 [27-41] and UTT: 35 [29-43]). Those with CD4 counts >500 cells/mm^3 were less likely to report a previous TB diagnosis (pre-UTT: 8% and UTT: 4%) than those with CD4 counts ≤500 cells/mm^3 (pre-UTT: 11% and UTT: 10%) but were slightly more likely to report alcohol use (pre-UTT: 46% and UTT: 42% for CD4 >500 cells/mm^3 vs pre-UTT: 41% and UTT: 37% for CD4 ≤500 cells/mm^3). Participants with higher CD4 counts were also more likely to report reaching the clinic on foot compared to a minibus taxi or other form of transportation (CD4>500 cells/mm^3 pre-UTT: 74% and UTT: 72% vs CD4 ≤500 pre-UTT: 65% and UTT: 62%) (Table 2.1).

Changes in ART initiation among those previously eligible

A total of 1,715 PLHIV were diagnosed with CD4 counts ≤500 cells/mm^3 across both cohorts and were eligible for ART initiation throughout the study period. Comparing before and after UTT implementation, ART initiation increased by 7.2% (95% CI: -2.3%, 16.7%) in this group (Table 2.2), and differential changes were observed by sex and age (Figure 2.3 and Table 2.3). The largest increase of 12.3% was observed among men (95% CI: 3.4%, 21.3%) while no increase was observed for women (RD: 3.2%; 95% CI: -8.8%, 15.3%). By age category, the greatest gain in ART uptake was observed among those 25-34 years old (RD: 10.1%; 95% CI: -1.5%, 21.7%) with a similar increase observed for those 35-44 years old (RD: 9.9%; 95% CI: -2.4%, 22.2%).

Difference-in-differences

Of all included participants, 2,271 (96%) had a CD4 count recorded at HIV diagnosis: 1,415 (62%) were diagnosed under the pre-UTT guidelines and 856

(38%) under the UTT guidelines. Among those eligible for ART initiation in both periods (CD4 ≤500 cells/mm^3) there was a small increase in 30-day initiation comparing the periods before and after implementation of UTT (51.5% vs. 58.6%) while there was a large increase (6.9% vs. 61.1%) for those newly eligible (CD4 >500 cells/mm^3) (Table 2.2). The median (IQR) CD4 count of those 24 individuals with a CD4 count >500 cells/mm^3 who initiated ART within 30 days under the pre-UTT guidelines was 575 (548-680) cells/mm^3, compared to 624 (561.5-788.5) cells/mm^3 for the 324 individuals who did not initiate within 30 days. Using difference-in-differences, removal of the CD4 eligibility threshold resulted in a 47.0% (95% CI: 35.1%, 58.9%) increase in ART uptake for PLHIV with CD4 counts >500 cells/mm^3 at diagnosis compared to those with CD4 ≤500 cells/mm^3. Inferences remained unchanged after adjustment for potential confounders (Table 2.2). In stratified analyses, the largest impact of UTT was observed for those aged ≥45 (difference-in-differences: 58.5%; 95% CI: 34.3%, 82.7%) as few participants initiated ART with a CD4 count >500 cells/mm^3 in the pre-UTT era (n=2/60; 3%) while ART initiation was similar to other age categories in the UTT era (n=18/28; 64%) (Table 2.3). However, results should be interpreted with caution as sample sizes were variable and confidence intervals were wide in stratified analyses.

Discussion

This study evaluated the impact of the shift to universal test and treat for HIV infection on ART initiation at high CD4 counts under routine conditions in South Africa. Few patients with CD4 counts >500 cells/mm^3 initiated ART prior to

the implementation of the UTT guidelines, indicating consistent application of guidelines at clinics. With the removal of the treatment eligibility threshold, we estimated an approximate 47% increase in ART uptake attributable to the change in guidelines among participants with CD4 counts >500 cells/mm^3 at diagnosis. Our results also demonstrated that expanding treatment eligibility did not result in reductions in ART uptake for those previously eligible. In addition, stratified analyses indicated that men, in particular, achieved gains in 30-day ART initiation among those with CD4 counts ≤500 cells/mm^3.

Our findings show an even greater impact of the removal of the treatment eligibility threshold than was expected based on a modeling study using data from KwaZulu-Natal.[19] While the authors estimated that 27% of PLHIV diagnosed with a CD4 >500 cells/mm^3 would initiate ART within 6 months under expanded eligibility guidelines,[19] our findings indicated that just over 60% had initiated by 30 days. Our results of a substantial impact of UTT are in line with recent research from Rwanda, where just 22% of patients had failed to initiate ART by 30 days under the UTT guidelines. The authors observed an overall 31% absolute increase in 30-day ART uptake compared to patients who enrolled in HIV care under pre-UTT guidelines and 95% of all patients who entered care under UTT initiated during the study period.[22]

Approximately 60% of patients initiated ART within 30 days under the UTT guidelines. This finding is similar to that reported in systematic reviews of studies published under lower eligibility thresholds from Sub-Saharan Africa which have estimated that between 63% and 68% of eligible individuals initiate ART.[23–25]

However, current national recommendations, released in September 2017, encourage same-day ART initiation for newly diagnosed PLHIV.[16] In a trial of same-day ART initiation compared to standard of care in South Africa, 97% of patients enrolled in the intervention arm initiated treatment within 90 days of study enrollment compared to 72% of patients initiated under standard of care.[26] Thus, if the results of this trial of same-day ART initiation translate to routine care, the initiation gap observed in our study, and in other settings, may be smaller under the current same-day ART initiation policy than during the period under study.

The results of this study should be interpreted in the context of several limitations. First, patients enrolled in intervention clinics had to provide additional blood samples for LTBI testing and after the completion of the blood draw and initial baseline questionnaire, patients had no further contact with study staff. Their inclusion in the parent cluster randomized trial, however, may have influenced their motivation to start ART which may have resulted in higher ART uptake than would be seen in a purely observational setting. In addition, as patients could enroll in the study up to 30 days after testing positive for HIV, patients may have been enrolled on return visits. This would bias our study population towards individuals who were more motivated to receive their CD4 count results and likely more motivated to start treatment than a general population of people testing in public sector facilities. As a result, our estimates of ART uptake and the impact of UTT may be greater than what would be observed in other settings. Second, we assumed that, if our study team could not locate a

file (electronic or paper) in the clinic for a study participant, then that participant did not initiate ART. However, filing systems varied by clinic, and our team may have missed files for participants which could have resulted in under-ascertainment of ART uptake. This may have biased the impact of UTT if this was differential over time or by CD4 count strata. Likewise, our estimates of ART uptake among pregnant women at 30 days (86%) and 90 days (89%) are lower than overall ART uptake for pregnant women reported for the Dr Kenneth Kaunda District in 2015/2016 (95.0%) and 2016/2017 (96.4%), which may also indicate under-ascertainment of ART uptake for our study participants, pregnant or otherwise.[20,27] Recent research from South Africa has also demonstrated that loss from a clinic in which a patient first initiates treatment is not equivalent to total loss from public-sector care, and "silent" transfers are common.[28] Thus, those individuals who did not initiate ART at the study clinic in which they were enrolled may have initiated treatment at another facility. This would render our results an under-estimate of total ART uptake and the impact of UTT may be greater than what we observed. Individuals who "silent" transfer may also not always disclose that they are aware of their status and may have previously received treatment when re-presenting for care. Hence, it is unclear to what extent patients enrolled in this study are truly newly diagnosed. Finally, approximately 34% of study participants never initiated ART during the follow-up period of TEKO which is likely a combination of silent transfer, loss from HIV care, and mortality after HIV diagnosis. However, ascertainment of mortality was low in our study. Among the total population of 2,365 men and non-pregnant

women enrolled, there were just 25 reported deaths (1.1%), 6 of which occurred prior to ART initiation (0.7% of non-initiators). Other studies have found higher rates of pre-treatment mortality. In a study from Cape Town, South Africa, 26% of ART-eligible patients who did not start ART died prior to initiation and estimates ranging from 8% to 18% have been reported in KwaZulu-Natal.[29–31] As such, some of the non-initiation observed may be attributable to unreported deaths, especially at lower CD4 counts. However, while our estimates of ART initiation may be subject to bias, as we abstracted data from routinely available information to create our study database, they are reflective of observational data and what records are available to clinical staff.

Conclusion

We observed a large increase in 30-day ART uptake after the removal of the treatment eligibility threshold for newly diagnosed, newly eligible PLHIV with CD4 counts >500 cells/mm^3 without a concomitant decrease for those previously eligible. However, overall ART uptake was sub-optimal, and a large proportion of patients were lost from initiation. The loss from initiation observed may be reduced under more recent same-day ART initiation recommendations, and our findings should be re-evaluated under those conditions. However, if gaps in ART uptake remain, innovative strategies to keep newly diagnosed PLHIV engaged with the health care system will likely be required to increase new initiations and reduce further morbidity and mortality.

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Table 2.1. Characteristics of 2,365 individuals newly diagnosed with HIV without active TB disease in 14 public sector primary healthcare facilities in North West Province, South Africa, January 2015 – May 2017

	Total n (%)	Pre-UTT n (%)			UTT n (%)		
Total		CD4 unknown	CD4 ≤500	CD4 >500	CD4 unknown	CD4 ≤500	CD4 >500
Sex and pregnancy	2365	62	1067	348	32	648	208
Male	947 (40%)	24 (39%)	463 (43%)	110 (32%)	13 (41%)	279 (43%)	58 (28%)
Female[1]	1418 (60%)	38 (61%)	604 (57%)	238 (68%)	19 (59%)	369 (57%)	150 (72%)
Age (years)							
Median (IQR)	33 (27-41)	30.5 (25-37)	34 (27-41)	31 (25-39.5)	31.5 (25-41.5)	35 (29-43)	30 (24-38.5)
18-24	387 (16%)	14 (23%)	157 (15%)	78 (22%)	6 (19%)	78 (12%)	54 (26%)
25-34	914 (39%)	28 (45%)	412 (39%)	134 (39%)	13 (41%)	243 (38%)	84 (40%)
35-44	637 (27%)	13 (21%)	314 (29%)	76 (22%)	7 (22%)	185 (29%)	42 (20%)
≥45	427 (18%)	7 (11%)	184 (17%)	60 (17%)	6 (19%)	142 (22%)	28 (13%)
Previous TB diagnosis							
No	2130 (90%)	51 (82%)	949 (89%)	320 (92%)	29 (91%)	582 (90%)	199 (96%)
Yes	235 (10%)	11 (18%)	118 (11%)	28 (8%)	3 (9%)	66 (10%)	9 (4%)
Education level							
Missing	3 (0%)	1 (2%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 0-5 or less	346 (15%)	8 (13%)	165 (15%)	57 (16%)	4 (13%)	96 (15%)	16 (8%)
Grade 6-11	1444 (61%)	36 (58%)	657 (62%)	207 (59%)	21 (66%)	405 (63%)	118 (57%)
Grade 12 or higher	572 (24%)	17 (27%)	243 (23%)	84 (24%)	7 (22%)	147 (23%)	74 (36%)
Employment status							
Missing	5 (0%)	0 (0%)	3 (0%)	0 (0%)	0 (0%)	2 (0%)	0 (0%)
Unemployed[2]	1282 (54%)	35 (56%)	554 (52%)	203 (58%)	14 (44%)	352 (54%)	124 (60%)
Employed	1078 (46%)	27 (44%)	510 (48%)	145 (42%)	18 (56%)	294 (45%)	84 (40%)
Total family income per month (ZAR)[3]							
Missing	27 (1%)	1 (2%)	22 (2%)	3 (1%)	0 (0%)	1 (0%)	0 (0%)
<1,000	777 (33%)	19 (31%)	333 (31%)	121 (35%)	11 (34%)	222 (34%)	71 (34%)
1,000-5,000	1265 (53%)	36 (58%)	586 (55%)	185 (53%)	14 (44%)	339 (52%)	105 (50%)

>5,000	296 (13%)	6 (10%)	126 (12%)	39 (11%)	7 (22%)	86 (13%)	32 (15%)
Household size (including respondent)							
Missing	5 (0%)	0 (0%)	1 (0%)	2 (1%)	0 (0%)	2 (0%)	0 (0%)
1 person	263 (11%)	5 (8%)	134 (13%)	31 (9%)	4 (13%)	69 (11%)	20 (10%)
2 people	468 (20%)	15 (24%)	188 (18%)	70 (20%)	6 (19%)	144 (22%)	45 (22%)
3-5 people	1155 (49%)	33 (53%)	527 (49%)	172 (49%)	18 (56%)	298 (46%)	107 (51%)
≥6 people	474 (20%)	9 (15%)	217 (20%)	73 (21%)	4 (13%)	135 (21%)	36 (17%)
Smoking status							
Missing	7 (0%)	0 (0%)	3 (0%)	3 (1%)	0 (0%)	1 (0%)	0 (0%)
Non-smoker[4]	1721 (73%)	42 (68%)	773 (72%)	246 (71%)	27 (84%)	485 (75%)	148 (71%)
Current smoker[5]	637 (27%)	20 (32%)	291 (27%)	99 (28%)	5 (16%)	162 (25%)	60 (29%)
Alcohol use							
Missing	7 (0%)	0 (0%)	6 (1%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Does not use alcohol	1402 (59%)	40 (65%)	625 (59%)	188 (54%)	17 (53%)	411 (63%)	121 (58%)
Uses alcohol	956 (40%)	22 (35%)	436 (41%)	159 (46%)	15 (47%)	237 (37%)	87 (42%)
Transportation to clinic							
Missing	15 (1%)	0 (0%)	10 (1%)	3 (1%)	0 (0%)	2 (0%)	0 (0%)
On foot	1554 (66%)	35 (57%)	692 (65%)	256 (74%)	18 (56%)	404 (62%)	149 (72%)
Minibus taxi or other[6]	796 (34%)	27 (44%)	365 (34%)	89 (26%)	14 (44%)	242 (37%)	59 (28%)
Travel time to clinic							
Missing	21 (1%)	1 (2%)	14 (1%)	4 (1%)	0 (0%)	1 (0%)	1 (0%)
≤15 minutes	767 (32%)	15 (24%)	371 (35%)	109 (31%)	10 (31%)	203 (31%)	59 (28%)
16-30 minutes	1047 (44%)	29 (47%)	459 (43%)	151 (43%)	18 (56%)	293 (45%)	97 (47%)
>30 minutes	530 (22%)	17 (27%)	223 (21%)	84 (24%)	4 (13%)	151 (23%)	51 (25%)

[1]Includes 89 women with unknown or missing pregnancy status
[2]Includes 76 students and 11 who reported 'other', including: 3 who reported receiving grants, 1 who reported a learnership, 6 pensioners, and 1 who did voluntary work
[3]Note 1 USD = 15.319 ZAR in 2016 (https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates)
[4]Includes 64 former smokers and 1657 never smokers
[5]Includes 533 daily smokers and 104 who smoke less than daily
[6]Includes 166 PLHIV who reported other forms of transportation: 26 who reported using a bicycle, 128 who reported a car or motorcycle, 6 who reported "tambai", 5 who reported NGO-provided or work-provided transport, and 1 who reported using a wheelchair

Figure 2.1. 30-day ART uptake stratified by CD4 count at diagnosis.

Dashed lines represent overall 30-day ART uptake during each time period (pre-UTT vs UTT) and points represent 30-day ART uptake within each quarter. Note there was a break in enrollment from July to August 2016 and enrollment was re-started in September 2016.

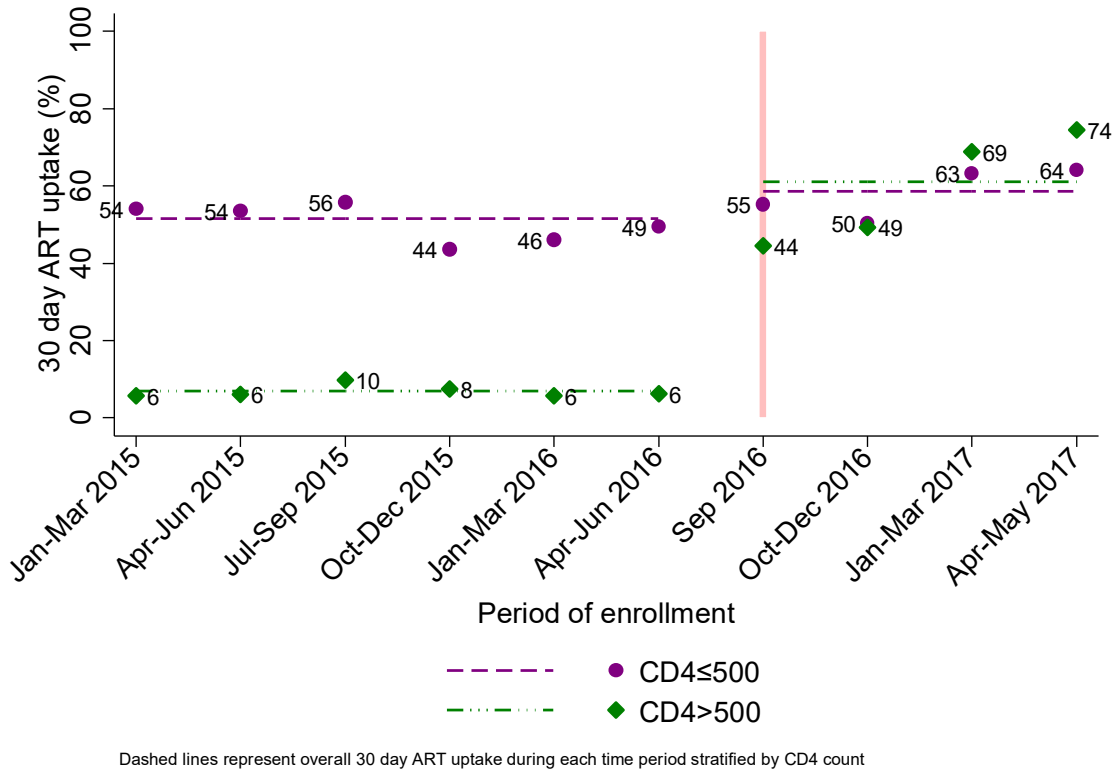

Table 2.2. Estimates of the association between 30-day ART uptake and guidelines under which an individual was diagnosed stratified by CD4 count

Characteristic	ART uptake/n (%) pre-UTT	ART uptake/n (%) UTT	RD (95% CI)[1]
CD4 count at HIV diagnosis			
CD4 ≤500 cells/mm^3	549/1067 (51.5%)	380/648 (58.6%)	7.2% (-2.3%, 16.7%)
CD4 >500 cells/mm^3	24/348 (6.9%)	127/208 (61.1%)	54.2% (44.3%, 64.0%)
Difference-in-differences			47.0% (35.1%, 58.9%)
Difference-in-differences[2]			46.7% (34.7%, 58.6%)

[1]Standard errors adjusted for clinic-level clustering
[2]Adjusted for all covariates (n=2,192)

Figure 2.2. 30-day ART uptake stratified by CD4 count at diagnosis, (a) sex and (b) age category

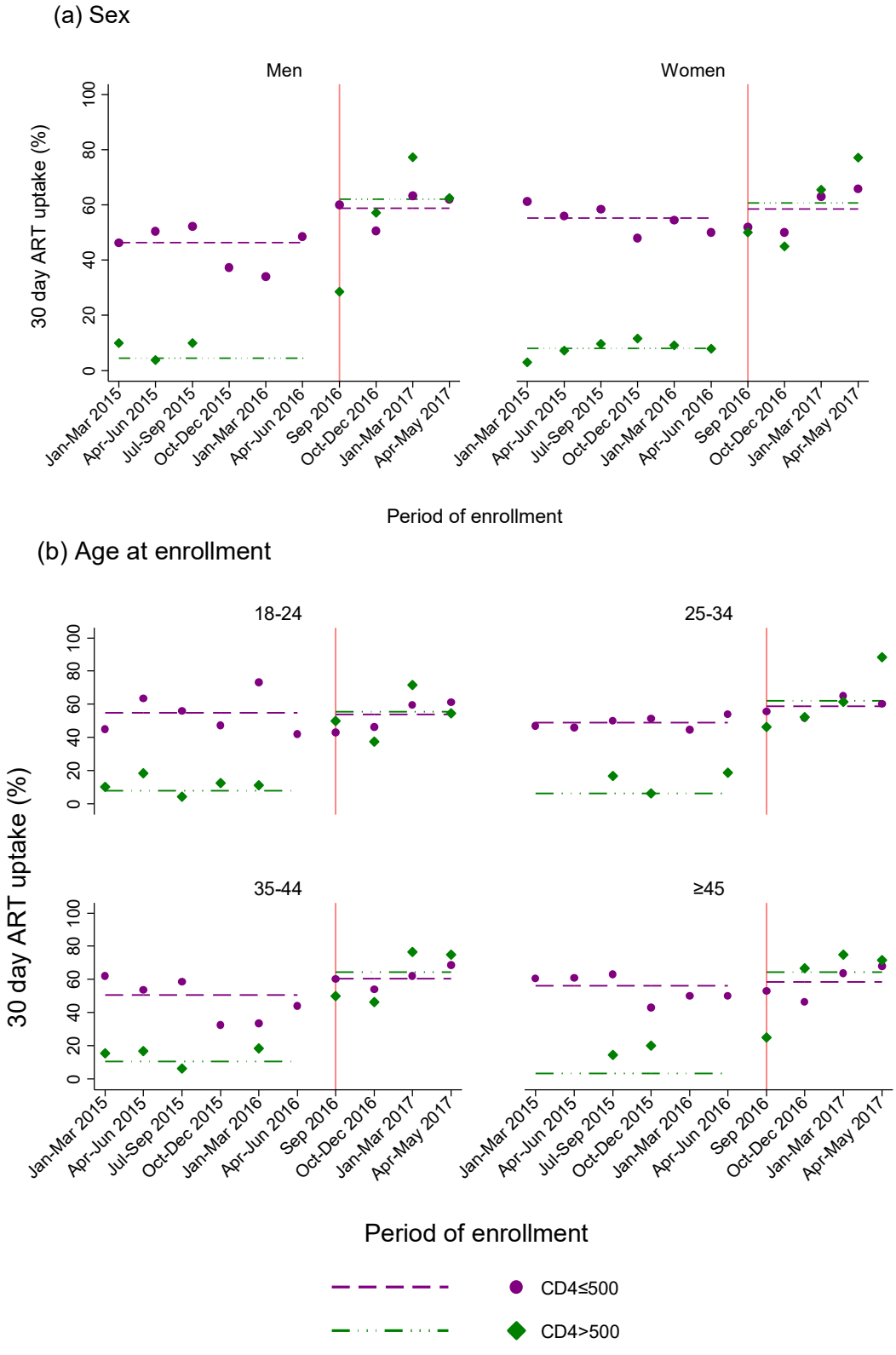

Table 2.3. Estimates of the association between 30-day ART uptake and guidelines under which an individual was diagnosed stratified by CD4 count, sex, and age category

Characteristic	ART uptake/n (%) pre-UTT	ART uptake/n (%) UTT	RD (95% CI)[1]
Sex: Men			
CD4 ≤500 cells/mm^3	215/463 (46.4%)	164/279 (58.8%)	12.3% (3.4%, 21.3%)
CD4 >500 cells/mm^3	5/110 (4.6%)	36/58 (62.1%)	57.5% (43.8%, 71.3%)
Difference-in-differences			45.2% (27.9%, 62.4%)
Difference-in-differences[2,3]			45.6% (27.2%, 64.1%)
Sex: Women			
CD4 ≤500 cells/mm^3	334/604 (55.3%)	216/369 (58.5%)	3.2% (-8.8%, 15.3%)
CD4 >500 cells/mm^3	19/238 (8.0%)	91/150 (60.7%)	52.7% (40.8%, 64.6%)
Difference-in-differences			49.4% (35.6%, 63.3%)
Difference-in-differences[2,4]			49.7% (34.5%, 64.9%)
Age: 18-24			
CD4 ≤500 cells/mm^3	86/157 (54.8%)	42/78 (53.9%)	-0.9% (-16.5%, 14.7%)
CD4 >500 cells/mm^3	6/78 (7.7%)	30/54 (55.6%)	47.9% (33.3%, 62.4%)
Difference-in-differences			48.8% (28.0%, 69.6%)
Difference-in-differences[2,5]			47.9% (25.8%, 69.9%)
Age: 25-34			
CD4 ≤500 cells/mm^3	201/412 (48.8%)	143/243 (58.9%)	10.1% (-1.5%, 21.7%)
CD4 >500 cells/mm^3	8/134 (6.0%)	52/84 (61.9%)	55.9% (39.1%, 72.7%)
Difference-in-differences			45.9% (27.4%, 64.3%)
Difference-in-differences[2,6]			45.6% (25.5%, 65.7%)

Age: 35-44			
CD4 ≤500 cells/mm^3	159/314 (50.6%)	112/185 (60.5%)	9.9% (-2.4%, 22.2%)
CD4 >500 cells/mm^3	8/76 (10.5%)	27/42 (64.3%)	53.8% (39.6%, 68.0%)
Difference-in-differences			43.9% (25.2%, 62.5%)
Difference-in-differences[2,7]			43.1% (24.2%, 62.0%)
Age: ≥45			
CD4 ≤500 cells/mm^3	103/184 (56.0%)	83/142 (58.5%)	2.5% (-10.7%, 15.7%)
CD4 >500 cells/mm^3	2/60 (3.3%)	18/28 (64.3%)	61.0% (41.7%, 80.2%)
Difference-in-differences			58.5% (34.3%, 82.7%)
Difference-in-differences[2,8]			57.3% (33.0%, 81.6%)

[1]Standard errors adjusted for clinic-level clustering
[2]Adjusted for all covariates
[3]n=879
[4]n=1,313
[5]n=355
[6]n=844
[7]n=596
[8]n=397

Chapter III: Changes in timing of HIV diagnosis, CD4 count at ART initiation, and ART uptake with the introduction of universal test and treat in South Africa

Abstract

Background: Perceived health status has been identified as a potential barrier to ART initiation. We evaluated change in health status (as defined by CD4 count) at HIV diagnosis and ART initiation, and the association between CD4 count and ART initiation before and after the introduction of universal test and treat (UTT) in South Africa.

Methods: We included non-pregnant adults (≥18) without tuberculosis who were diagnosed with HIV between January 2015-May 2017 at 14 clinics. We used quantile (median) regression to estimate the change in CD4 count at 1) diagnosis and 2) ART initiation before and after implementation of UTT. We used Poisson regression to evaluate the association between CD4 count and 30-day ART initiation, stratified by pre-/post-UTT. Results are presented as the difference in median CD4 count or risk ratio (RR) with 95% confidence intervals (CI), estimated using cluster-robust standard errors.

Results: The median (interquartile range) CD4 count of 2,192 included participants was 315.5 (168-496) cells/mm^3. After adjustment, no difference in CD4 count at diagnosis was observed for UTT versus pre-UTT (6.7; 95% CI: -18.1, 31.2) while a clinically meaningful increase was observed at ART initiation (92.9; 95% CI: 54.0, 131.8). Compared to patients with CD4 counts between 51-200, patients diagnosed with CD4 counts between 351-500 were less likely to initiate ART under pre-UTT (aRR: 0.79; 95% CI: 0.64, 0.97) while no association was observed under UTT.

Conclusions: No association was observed between CD4 count category at diagnosis and ART initiation under UTT, indicating that the treat all policy has resulted in similar initiation rates for all people living with HIV.

Introduction

Over the last several years, major changes to HIV treatment guidelines have been recommended by the World Health Organization (WHO) to encourage earlier HIV diagnosis and treatment initiation in order to reduce morbidity and mortality for people living with HIV (PLHIV). In 2015, the WHO recommended removal of CD4 count-based treatment eligibility thresholds and adoption of a universal test and treat (UTT) approach.[1] The South African National Department of Health (NDoH), which provides treatment to the world's largest number of PLHIV, with over 90% of ART provision occurring in the public sector,[2,3] adopted the WHO's recommendations in September 2016.[4] This policy change opened up access to treatment to all diagnosed with HIV regardless of CD4 count, the presence or absence of comorbidities, or pregnancy.

The changes to South Africa's HIV treatment guidelines were made to support achievement of the UNAIDS 90-90-90 targets in which 90% of PLHIV are diagnosed, 90% of those diagnosed are on treatment, and 90% of those on treatment are virologically suppressed.[4,5] According to the most recent national HIV estimates, 90.5% of PLHIV in South Africa are aware of their status, 68.4% with known status are on antiretroviral therapy (ART), and 88.4% of those on ART have achieved virologic suppression (defined as viral load <1000 copies/mL).[6] Based on these findings, South Africa has achieved the first goal of the 90-90-90 targets and is within reach of the third. However, despite a successful prevention of mother-to-child transmission program in which 95.1% of pregnant women were reported to have initiated ART during antenatal care in

2016/2017,[7] ART uptake among men and non-pregnant women remains short of targets. In addition, recent research of a national laboratory-based cohort in South Africa has also shown that diagnosis still often occurs late in the course of infection, after CD4 counts have fallen below 200 cells/mm^3, especially among men.[8]

Late diagnosis and delayed initiation of ART is associated with reduced life expectancy and increased risk of comorbidities.[9–14] However, qualitative research in resource-limited settings has raised concerns that asymptomatic PLHIV may be hesitant to initiate ART because they have not yet experienced physical or clinical manifestations of their HIV infection.[15–17] Reduced rates of ART initiation at higher CD4 counts under previous iterations of South Africa's HIV treatment guidelines have also been noted in quantitative studies.[18,19] Thus, in this analysis we sought to estimate change in 1) timing of HIV diagnosis (using CD4 count as a proxy measure) and 2) CD4 count at ART initiation before and after implementation of UTT, and 3) assess the association between CD4 count at diagnosis and ART uptake.

Methods

Study sites

We collected data from 14 public sector clinics in the Dr. Kenneth Kaunda District of North West province. These facilities participated in a cluster randomized trial (TEKO) to evaluate the Quantiferon Gold In-Tube test (QGIT), an interferon-γ release assay, and the tuberculin skin test for the diagnosis of

latent TB infection and uptake of isoniazid preventive therapy in PLHIV. HIV prevalence in Dr. Kenneth Kaunda District is estimated at 12.9%,[7] and treatment in public sector facilities is provided according to NDoH guidelines. The period of this analysis covered the 2015 and 2016 NDoH guidelines. From January 2015 to August 2016, HIV treatment was provided to 1) PLHIV based on the presence of severe comorbidities (i.e., a WHO stage 3 or 4 disease, active TB disease, or hepatitis B co-infection); 2) pregnant or breastfeeding women; and 3) those with a CD4 count ≤500 cells/mm^3.[20] Starting in September 2016, barriers to treatment initiation were removed, and all PLHIV were eligible for ART.[4]

Study population

All men and non-pregnant women enrolled in TEKO between January 2015 and May 2017 were eligible for inclusion in these analyses. Eligible participants were required to be 18 years of age or older, newly diagnosed with HIV (i.e., study enrollment had to occur within 30 days of HIV diagnosis), and eligible for IPT (i.e., no excessive alcohol use, symptoms of peripheral neuropathy, or active TB disease). Participants who enrolled but had no evidence that their files were attempted to be found were excluded from analyses (n=30). We also excluded participants who were later determined to have prior knowledge of their HIV status, as indicated by a clinic visit, CD4 count, or viral load more than 30 days prior to study enrollment or a suppressed (<400 copies/mL) baseline viral load (defined as prior to or within 7 days of either study enrollment or ART initiation) (n=331). Participants who were enrolled but later determined to have TB disease at the time of study enrollment were also

excluded (n=64); as were participants with no age recorded (n=5) and those for whom the ART initiation date was recorded prior to the earliest of study enrollment or the first CD4 count date (n=18).

After consenting to enroll, patients participated in a baseline questionnaire administered by study staff member. Data collected as part of the screening and enrollment process and used in this analysis included: age (categorized as 18-24, 25-34, 35-44, ≥45); sex and pregnancy status; education level (grade 0-5 or less, grade 6-11, grade 12 or higher) and employment status (employed or unemployed); family income level (<1,000 ZAR, 1,000-5,000 ZAR, >5,000 ZAR); the number of individuals living in the household (1 person, 2 people, 3-5 people, ≥6 people); travel time to the clinic (≤15 minutes, 16-30 minutes, >30 minutes) and mode of transportation used (walking versus minibus taxi or other) to reach the clinic; and alcohol (yes/no) and tobacco usage (never or former smoker versus current smoker). After the baseline interview and blood draw for QGIT testing for participants in the intervention arm, participants were followed through their medical records, which included both paper and electronic data sources. Information obtained from medical records included clinic visit dates, laboratory test results, and the date of ART initiation. Data were collected using REDCap (Research Electronic Data Capture) hosted at Johns Hopkins University.[21]

Variable definitions

Upon diagnosis with HIV, individuals are referred for a blood draw for CD4 count staging, which typically occurs on the same day as diagnosis. As patients were enrolled up to 30 days after HIV diagnosis, we defined the “first known

date" as the earliest of study enrollment or the first CD4 count date as a proxy for the HIV diagnosis date. Patients for whom the first known date was between January 2015 and June 2016, when a break in study enrollment occurred, were categorized as diagnosed under the pre-UTT guidelines while those for whom the first known date was between September 2016 and May 2017, when study enrollment closed, were considered to have been diagnosed under the UTT guidelines. CD4 count at diagnosis was defined as the earliest recorded CD4 count between 30 days prior to and 30 days after study enrollment and timely ART initiation was defined to have occurred within 30 days of the first known date. Patients for whom files could not be found or where a record was found but no further visits were documented were assumed to have not started ART.

Statistical analysis

For the first and second objectives, we sought to estimate the change in 1) CD4 count at diagnosis and 2) CD4 count at ART initiation before and after implementation of UTT. For both of these objectives, we used quantile (median) regression to estimate the change in median CD4 count. Results are presented as the difference in median CD4 count with corresponding 95% confidence intervals (CI). For the second objective, the analysis was restricted to only those individuals who initiated ART within 30 days of the first known date. In order to evaluate whether results differed by sex or age, we also present stratified results estimated using an interaction term between sex or age category and period of enrollment.

For the third objective, we evaluated whether 30-day ART uptake differed by CD4 count stratum at HIV diagnosis among those eligible for ART under each set of guidelines (pre-UTT vs UTT). CD4 count at diagnosis was defined as ≤50, 51-200, 201-350, 351-500, and >500 cells/mm^3. As patients with CD4 counts >500 cells/mm^3 were only eligible for initiation with a WHO Stage 3 or 4 disease under the pre-UTT guidelines, we excluded these patients from the analysis for the pre-UTT period. Poisson regression was used to evaluate the association between CD4 count and ART initiation, and results are presented as risk ratios (RR) with corresponding 95% CI.

As a sensitivity analysis, we also evaluated the association between CD4 count stratum and ART initiation within 90 days of the first known date among those eligible for ART initiation under each set of guidelines. This analysis was restricted to only those individuals with at least 90 days of follow-up recorded after the first known date (based on either a recorded clinic visit or evidence that a file was attempted to be found after 90 days). We used complete case analyses for all unadjusted and adjusted regression models and accounted for clustering by clinic using cluster robust standard errors. Covariates were chosen *a priori* as potential confounders of timing of HIV diagnosis and ART initiation based on the literature and all were included in adjusted models.

Ethical approval

Ethical approval was obtained from the Institutional Review Board of the Johns Hopkins University School of Medicine and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Results

Between January 2015 and May 2017, 2,965 individuals newly diagnosed with HIV were enrolled in TEKO and 20% (n=600) were women diagnosed during pregnancy who were excluded from further analyses. The median (interquartile range [IQR]) age at HIV diagnosis of the remaining 2,365 participants was 33 (27-41) years. Approximately 60% of participants were female, 10% reported a previous TB diagnosis, just over a quarter (27%) reported being current smokers, and 40% reported using alcohol. More than half of participants were unemployed (54%), and 33% reported a total family income of less than 1,000 ZAR per month (65 USD based on 2016 average exchange rate) (Table 3.1).[22]

Timing of HIV diagnosis before and after implementation of UTT

Of the 2,365 PLHIV included, most (62%) were enrolled prior to the implementation of the UTT guidelines, and no meaningful differences were observed between the individuals enrolled before and after the guidelines changed (Table 3.1). After exclusion of participants without CD4 count at HIV diagnosis (n=94) and those missing data on other covariates (n=79), 2,192 PLHIV were included. The median (IQR) CD4 count at diagnosis was 315.5 cells/mm^3 (168-496) and no change in median CD4 at diagnosis was observed between the two sets of guidelines before (-3.0 cells/mm^3; 95% CI: -31.6, 25.6) or after (6.7 cells/mm^3; 95% CI: -18.1, 31.2) adjustment for covariates (Figure 3.1).

Women were diagnosed with a higher median CD4 count (340 cells/mm^3; IQR: 179-537) than men (282 cells/mm^3; IQR: 144-440). Participants ages 18-24 were diagnosed earliest in the course of infection with a median (IQR) CD4 of

418 cells/mm^3 (IQR: 279-580), followed by participants ages 25-34 (326 cells/mm^3; IQR: 172-507). Those diagnosed between the ages of 35-44 (266 cells/mm^3; IQR: 133.5-434) and at 45 years of age or older (269 cells/mm^3; IQR: 137-464) had similar median CD4 counts at diagnosis. In adjusted analyses, no clinically meaningful changes were observed in CD4 count at diagnosis when stratified by sex or age (Figure 3.1).

CD4 count at ART initiation before and after implementation of UTT

The removal of the CD4 eligibility threshold allowed newly diagnosed PLHIV with CD4 counts at diagnosis >500 cells/mm^3 to initiate treatment. Prior to the implementation of these guidelines, 39% (n=575/1477) of participants initiated ART within 30 days of the first known date. After implementation of the guidelines, 30-day ART uptake increased to 58% (n=512/888). Among 1051 participants with a CD4 count at ART initiation and full covariate data (97%), the median (IQR) CD4 count at ART initiation in the pre-UTT era was 222 cells/mm^3 (129.5-364.5) and was 309 cells/mm^3 (167-509) in the UTT era. This resulted in an increase of 87.0 cells/mm^3 (95% CI: 49.3, 124.7), with no change to inferences when adjusted for covariates (difference: 92.9 cells/mm^3; 95% CI: 54.0, 131.8) (Figure 3.2).

Differential changes in median CD4 count at ART initiation were observed by sex and age. After adjustment for baseline covariates, median CD4 count at ART initiation increased by 121.0 cells/mm^3 (95% CI: 60.9, 181.1) for women and by 40.0 cells/mm^3 (95% CI: -1.4, 81.4) for men (Figure 3.2). Adjusted increases in median CD4 count at ART initiation of at least 100 cells/mm^3 were reached

among participants ages 18-24 (123.5 cells/mm^3; 95% CI: 50.9, 196.1), 25-34 (101.8; 95% CI: 46.1, 157.4) and those 45 years of age and older (131.4 cells/mm^3; 95% CI: 76.7, 186.2) while the increase for those ages 35 to 44 was not clinically meaningful (30.5; 95% CI: -13.5, 74.6) (Figure 3.2).

The association between CD4 count at diagnosis and ART initiation

Almost one-third (30%) of study participants were diagnosed late in the course of their infection with CD4 counts ≤200 cells/mm^3, and approximately 6% had a CD4 count ≤50 cells/mm^3. Compared to individuals with CD4 counts >500 cells/mm^3, those with CD4 counts ≤50 cells/mm^3 were more likely to be men (48% vs 30%), were slightly older (median [IQR] age: 37 [31-45] vs 31 [25-39]), and were more likely to report a previous TB diagnosis (16% vs 7%). These patients were also were slightly less likely to report being unemployed (51% vs 59%), were less likely to report using alcohol (28% vs 44%), and were less likely to walk to the clinic (57% vs 73%) (Appendix Table 3.1).

In the pre-UTT cohort, 1011 individuals were eligible for ART initiation (CD4 ≤500) and had full covariate information. Overall, 52% initiated ART within 30 days. Patients diagnosed with a CD4 count between 201-350 (RR: 0.81; 95% CI: 0.74, 0.89) and those diagnosed with a CD4 count between 351-500 (RR: 0.82; 95% CI: 0.67, 1.00) were less likely to initiate ART within 30 days than those diagnosed with a CD4 count between 51-200. After adjustment for potential confounders, the results remained unchanged, and patients with higher CD4 counts remained approximately 20% less likely to initiate than those with CD4 counts between 51-200. However, ART initiation within CD4 count strata

fluctuated over time and the observed association was not consistent across 6-monthly intervals (Appendix Figure 3.1) In addition, in an adjusted model, we observed an increased risk of ART initiation for women vs men (adjusted RR [aRR]: 1.28; 95% CI: 1.03, 1.59) and noted a slightly increased risk of initiation for those with a previous TB diagnosis (aRR: 1.16; 95% CI: 0.98, 1.37).

After implementation of the UTT guidelines, no association was observed between CD4 count stratum and ART uptake among 846 included patients. Patients with a CD4 count >500 cells/mm^3 were as likely to initiate ART within 30 days (61%) as those with a CD4 count between 51-200 cells/mm^3 (62%) (aRR: 1.00; 95% CI: 0.81, 1.25); as were those with a CD4 count between 351-500 (aRR: 0.95; 95% CI: 0.79, 1.14). Likewise, no association was observed for sex or previous TB diagnosis. However, there was an increased risk of ART initiation for patients who reported a total family income >5,000 ZAR per month (aRR: 1.45; 95% CI: 1.18, 1.78) or between 1,000-5,000 ZAR per month (aRR: 1.20; 95% CI: 1.03, 1.40) compared to those reporting <1000 ZAR (Table 3.2). Similar results were observed in a sensitivity analysis evaluating the association between CD4 count at diagnosis and ART initiation within 90 days (Table 3.3).

Discussion

With the update to HIV treatment guidelines released in 2016 which called for universal eligibility for ART, South Africa has positioned itself to be able to achieve the second goal of the UNAIDS 90-90-90 targets, 90% uptake of ART. Our findings showed that CD4 counts at HIV diagnosis remained stable before and after implementation of UTT. With the removal of the ART-eligibility

threshold, a clinically significant increase in CD4 count at ART initiation was achieved in our study clinics under routine care. Moreover, patients with higher CD4 counts (>200 cells/mm^3) were less likely to initiate ART within 30 and 90 days under previous guidelines. These associations were no longer observed under UTT, indicating that implementation of universal treatment has resulted in similar initiation rates for all PLHIV.

The 2017 Human Sciences Research Council national HIV prevalence survey indicated that women were more likely to be aware of their status (88.9% vs 78.0%) than men.[23] This may be a reflection of high uptake of HIV testing by women during antenatal care. However, our findings also demonstrated that non-pregnant women are identified earlier in the course of HIV infection than men, similar to findings reported elsewhere in the literature,[8,19,24,25] which may be a reflection of greater contact with the health care system generally for women. Likewise, as those diagnosed with CD4 counts >500 cells/mm^3 were more likely to be women (70% vs 30%), we observed a larger increase in median CD4 at ART initiation for women compared to men, including after adjustment for potential confounders. Overall, median CD4 count at ART initiation for those who initiated within 30 days increased by approximately 90 cells/mm^3, breaking the 300 cells/mm^3 mark under the UTT guidelines. With increasing numbers of relatively healthy patients initiating ART, decongestion strategies to encourage stable patients to access care through down referral programs and off-site ART pickup will be important to ensure that healthcare providers can focus on patients with complicated clinical needs.

While overall 30-day ART uptake under the UTT guidelines in this study was below what is required to achieve the UNAIDS 90-90-90 goals, our findings did not indicate that having a high CD4 count at ART initiation was a barrier to treatment uptake under the UTT guidelines. Our finding that higher CD4 counts were associated with lower rates of ART uptake under the pre-UTT guidelines is in line with research conducted when CD4 count-based treatment eligibility thresholds were in place.[18,19,24,26,27] However, recent research from Rwanda conducted under UTT guidelines has also indicated no association between CD4 count stratum and 30-day ART uptake.[28] Given that severity of illness is no longer a consideration for ART initiation, these recent findings that failed to observe an association between CD4 count and ART uptake may represent a response to the shift in messaging around ART initiation as no longer being solely for those individuals 'sick enough' to need it but for all PLHIV.

Approximately 25% of our study participants were diagnosed with CD4 counts >500 cells/mm^3, and increased effort will be required to engage undiagnosed PLHIV with the healthcare system to increase earlier diagnosis and treatment initiation. Previous research has indicated that individuals tested as part of outreach programs through mobile testing services are diagnosed with higher CD4 counts and, thus, are more likely to be asymptomatic than those who test through clinic-based HCT services.[29–31] However, linkage to care from mobile testing services tends to be lower than clinic-based testing.[29–31] Improving linkage to care from mobile testing services and/or increasing uptake of routine clinic-based testing of otherwise asymptomatic individuals will be important for

improving the general health status of individuals at diagnosis and ART initiation in order to reduce morbidity associated with delayed ART uptake.

The results of this study should be viewed in light of several limitations. While the proportion of patients without a CD4 count recorded was low in our study, some bias may exist from excluding those patients without a CD4 count, or other missing data, from analyses. In addition, patients could be enrolled in the parent cluster randomized trial up to 30 days after testing HIV positive. As the period directly after receipt of a positive HIV test result is a period of high risk for loss from care, patients enrolled in this study upon a return clinic visit after HIV diagnosis may be more motivated to receive their CD4 count result and initiate treatment than the general population of people who test positive for HIV. Likewise, while there was no further interaction between study staff and patients after the initial baseline interview and QGIT blood draw (for participants at intervention clinics), enrollment into the parent cluster randomized trial may have had an impact on patients' engagement in care compared to a general population of patients newly diagnosed with HIV. Thus, our estimates of ART uptake may be biased compared to what would have been observed in the absence of the parent trial. Finally, not all patients who were diagnosed with HIV during the study period at these 14 facilities were enrolled in the trial; due to trial exclusion criteria, availability of study staff for patient enrollment, or patient refusal to participate. Thus, the patients who did enroll in this study may not be representative of all patients diagnosed during this time which may limit the generalizability of our findings.

Conclusion

With removal of ART eligibility criteria under UTT, we observed a clinically significant increase in median CD4 count at ART initiation for those who initiated within 30 days compared to previous guidelines. While patients diagnosed with higher CD4 counts were less likely to initiate ART under the pre-UTT guidelines, this association no longer held under UTT and similar levels of ART uptake were observed across all CD4 count categories. Increasing patient populations at individual clinics may stretch an already over-burdened public health system. Thus, promoting clinic decongestion strategies for stable patients may be important to allow clinic staff to focus on more complicated clinical cases.

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Table 3.1. Baseline characteristics of newly diagnosed PLHIV without active TB disease

Patients were enrolled at 14 public sector healthcare facilities in North West Province, South Africa between January 2015 – May 2017 and characteristics are stratified according to the guidelines under which a patient enrolled in the study (pre-UTT or UTT).

	Total n (%)	Pre-UTT n (%)	UTT n (%)
Total	2365	1477 (62%)	888 (38%)
Baseline CD4 count			
Median (IQR) n	314 (168-494)	314 (168-495)	313 (170-488)
Missing	94 (4%)	62 (4%)	32 (4%)
≤50	145 (6%)	85 (6%)	60 (7%)
51-200	576 (24%)	368 (25%)	208 (23%)
201-350	543 (23%)	333 (23%)	210 (24%)
351-500	451 (19%)	281 (19%)	170 (19%)
>500	556 (24%)	348 (24%)	208 (23%)
Sex and pregnancy			
Male	947 (40%)	597 (40%)	350 (39%)
Female[1]	1418 (60%)	880 (60%)	538 (61%)
Age (years)			
Median (IQR) n	33 (27-41)	33 (27-41)	33 (27-42)
18-24	387 (16%)	249 (17%)	138 (16%)
25-34	914 (39%)	574 (39%)	340 (38%)
35-44	637 (27%)	403 (27%)	234 (26%)
≥45	427 (18%)	251 (17%)	176 (20%)
Previous TB diagnosis			
No	2130 (90%)	1320 (89%)	810 (91%)
Yes	235 (10%)	157 (11%)	78 (9%)
Education level			
Missing	3 (0%)	3 (0%)	0 (0%)
Grade 0-5 or less	346 (15%)	230 (16%)	116 (13%)
Grade 6-11	1444 (61%)	900 (61%)	544 (61%)
Grade 12 or higher	572 (24%)	344 (23%)	228 (26%)
Employment status			
Missing	5 (0%)	3 (0%)	2 (0%)
Unemployed[2]	1282 (54%)	792 (54%)	490 (55%)
Employed	1078 (46%)	682 (46%)	396 (45%)
Total family income per month (ZAR)[3]			
Missing	27 (1%)	26 (2%)	1 (0%)

<1,000	777 (33%)	473 (32%)	304 (34%)
1,000-5,000	1265 (54%)	807 (55%)	458 (52%)
>5,000	296 (13%)	171 (12%)	125 (14%)
Household size (including respondent)			
Missing	5 (0%)	3 (0%)	2 (0%)
1 person	263 (11%)	170 (12%)	93 (10%)
2 people	468 (20%)	273 (18%)	195 (22%)
3-5 people	1155 (49%)	732 (50%)	423 (48%)
≥6 people	474 (20%)	299 (20%)	175 (20%)
Smoking status			
Missing	7 (0%)	6 (0%)	1 (0%)
Non-smoker[4]	1721 (73%)	1061 (72%)	660 (74%)
Current smoker[5]	637 (27%)	410 (28%)	227 (26%)
Alcohol use			
Missing	7 (0%)	7 (0%)	0 (0%)
Does not use alcohol	1402 (59%)	853 (58%)	549 (62%)
Uses alcohol	956 (40%)	617 (42%)	339 (38%)
Transportation to clinic			
Missing	15 (1%)	13 (1%)	2 (0%)
On foot	1554 (66%)	983 (67%)	571 (64%)
Minibus taxi or other[6]	796 (34%)	481 (33%)	315 (35%)
Travel time to clinic			
Missing	21 (1%)	19 (1%)	2 (0%)
≤15 minutes	767 (32%)	495 (34%)	272 (31%)
16-30 minutes	1047 (44%)	639 (43%)	408 (46%)
>30 minutes	530 (22%)	324 (22%)	206 (23%)

[1]Includes 89 women with unknown or missing pregnancy status
[2]Includes 76 students and 11 who reported 'other', including: 3 who reported receiving grants, 1 who reported a learnership, 6 pensioners, and 1 who did voluntary work
[3]Note 1 USD = 15.319 ZAR in 2016 (https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates)
[4]Includes 64 former smokers and 1657 never smokers
[5]Includes 533 daily smokers and 104 who smoke less than daily
[6]Includes 166 PLHIV who reported other forms of transportation: 26 who reported using a bicycle, 128 who reported a car or motorcycle, 6 who reported "tambai", 5 who reported NGO-provided or work-provided transport, and 1 who reported using a wheelchair

Figure 3.1. Change in median CD4 count (cells/mm^3) at HIV diagnosis before and after the implementation of the UTT guidelines

The figure depicts the point estimate and 95% confidence interval comparing median CD4 count at diagnosis in the UTT period to the pre-UTT period, controlling for all other covariates. Results stratified by sex and age category were estimated using an interaction term in quantile (median) regression models. Cluster-robust standard errors were used to compute 95% confidence intervals.

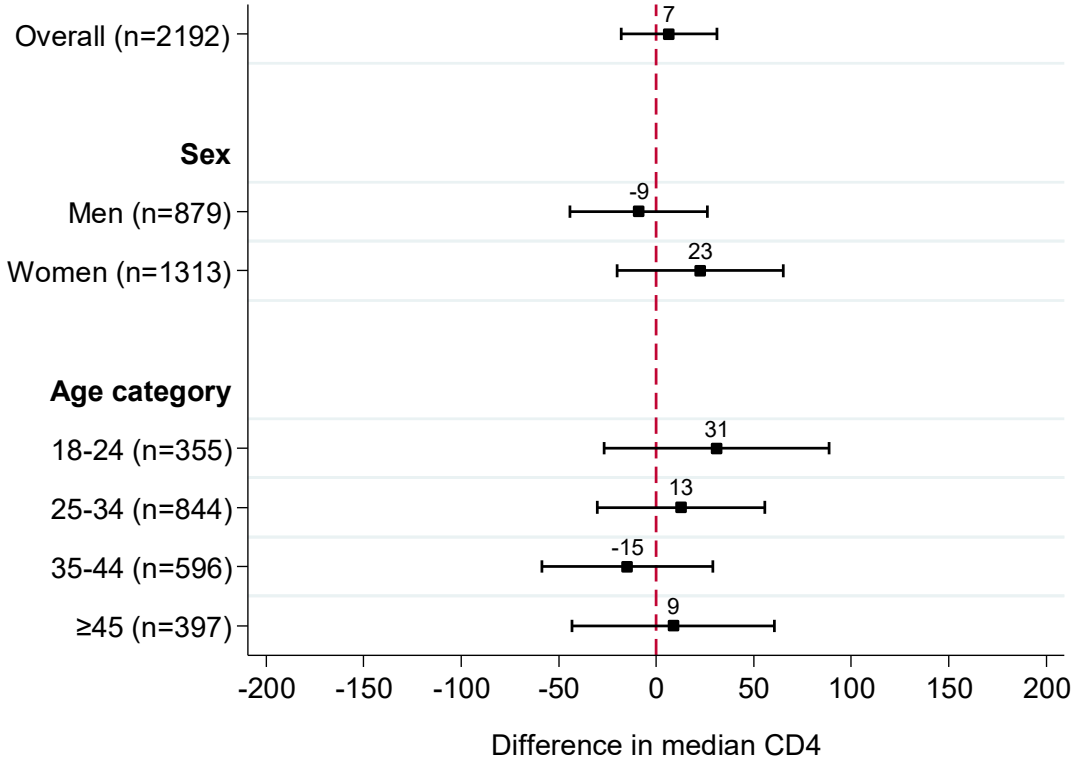


Figure 3.2. Change in median CD4 count (cells/mm^3) at ART initiation before and after the implementation of the UTT guidelines

The figure depicts the point estimate and 95% confidence interval comparing median CD4 count at ART initiation in the UTT period to the pre-UTT period controlling for all other covariates. Only participants who initiated ART within 30 days of the first known date are included. Results stratified by sex and age category were estimated using an interaction term in quantile (median) regression models. Cluster-robust standard errors were used to compute 95% confidence intervals.

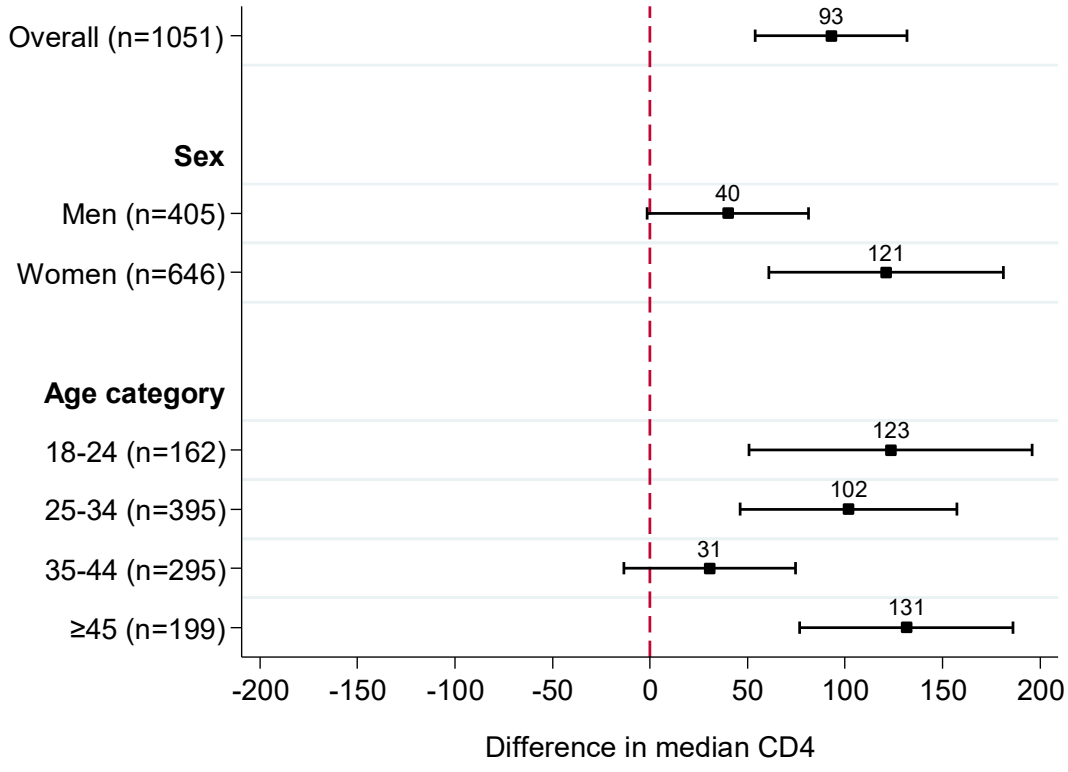


Table 3.2 Unadjusted and adjusted estimates of 30-day ART uptake, stratified by period of enrollment

	Pre-UTT Cohort (n=1,011)			UTT Cohort (n=846)		
	ART uptake/n (%)	RR (95% CI)	aRR (95% CI)	ART uptake/n (%)	RR (95% CI)	aRR (95% CI)
CD4 count (cells/mm^3)						
≤50	42/81 (51.9%)	0.88 (0.70, 1.11)	0.85 (0.66, 1.10)	37/59 (62.7%)	1.02 (0.83, 1.25)	1.06 (0.89, 1.25)
51-200	204/348 (58.6%)	Reference	Reference	127/206 (61.7%)	Reference	Reference
201-350	149/314 (47.5%)	0.81 (0.74, 0.89)	0.81 (0.73, 0.89)	114/207 (55.1%)	0.89 (0.76, 1.05)	0.91 (0.76, 1.08)
351-500	129/268 (48.1%)	0.82 (0.67, 1.00)	0.79 (0.64, 0.97)	97/167 (58.1%)	0.94 (0.79, 1.12)	0.95 (0.79, 1.14)
>500	--	--	--	127/207 (61.4%)	1.00 (0.83, 1.19)	1.00 (0.81, 1.25)
Sex						
Male	201/438 (45.9%)	Reference	Reference	198/333 (59.5%)	Reference	Reference
Female	323/573 (56.4%)	1.23 (1.05, 1.44)	1.28 (1.03, 1.59)	304/513 (59.3%)	1.00 (0.88, 1.12)	1.05 (0.92, 1.21)
Age (years)						
18-24	83/149 (55.7%)	Reference	Reference	72/131 (55.0%)	Reference	Reference
25-34	195/393 (49.6%)	0.89 (0.78, 1.01)	0.90 (0.77, 1.05)	192/322 (59.6%)	1.08 (0.90, 1.31)	1.07 (0.88, 1.30)
35-44	150/298 (50.3%)	0.90 (0.74, 1.10)	0.90 (0.70, 1.16)	137/224 (61.2%)	1.11 (0.95, 1.30)	1.10 (0.93, 1.29)
≥45	96/171 (56.1%)	1.01 (0.85, 1.19)	0.98 (0.79, 1.23)	101/169 (59.8%)	1.09 (0.85, 1.39)	1.06 (0.83, 1.37)
Previous TB diagnosis						
No	460/900 (51.1%)	Reference	Reference	459/773 (59.4%)	Reference	Reference
Yes	64/111 (57.7%)	1.13 (0.98, 1.30)	1.16 (0.98, 1.37)	43/73 (58.9%)	0.99 (0.77, 1.27)	1.00 (0.78, 1.28)
Education level						
Grade 0-5 or less	82/152 (54.0%)	Reference	Reference	68/110 (61.8%)	Reference	Reference
Grade 6-11	311/625 (49.8%)	0.92 (0.81, 1.05)	0.93 (0.79, 1.10)	294/518 (56.8%)	0.92 (0.75, 1.13)	0.90 (0.72, 1.13)
Grade 12 or higher	131/234 (56.0%)	1.04 (0.86, 1.26)	1.06 (0.84, 1.35)	140/218 (64.2%)	1.04 (0.82, 1.31)	0.98 (0.77, 1.24)
Employment status						
Unemployed	272/523 (52.0%)	Reference	Reference	273/470 (58.1%)	Reference	Reference
Employed	252/488 (51.6%)	0.99 (0.90, 1.10)	1.06 (0.94, 1.21)	229/376 (60.9%)	1.05 (0.96, 1.14)	0.93 (0.82, 1.05)

Total family income per month (ZAR)						
<1,000	164/321 (51.1%)	Reference	Reference	149/292 (51.0%)	Reference	Reference
1,000-5,000	293/567 (51.7%)	1.01 (0.88, 1.16)	1.01 (0.87, 1.17)	267/438 (61.0%)	1.19 (1.04, 1.37)	1.20 (1.03, 1.40)
>5,000	67/123 (54.5%)	1.07 (0.87, 1.30)	1.03 (0.80, 1.34)	86/116 (74.1%)	1.45 (1.23, 1.72)	1.45 (1.18, 1.78)
Household size (including respondent)						
1 person	58/121 (47.9%)	Reference	Reference	51/88 (58.0%)	Reference	Reference
2 people	94/176 (53.4%)	1.11 (0.90, 1.37)	1.08 (0.88, 1.33)	122/187 (65.2%)	1.13 (0.90, 1.41)	1.12 (0.88, 1.43)
3-5 people	272/509 (53.4%)	1.11 (0.89, 1.40)	1.08 (0.89, 1.33)	225/403 (55.8%)	0.96 (0.77, 1.20)	0.97 (0.76, 1.25)
≥6 people	100/205 (48.8%)	1.02 (0.80, 1.30)	0.97 (0.77, 1.20)	104/168 (61.9%)	1.07 (0.83, 1.37)	1.07 (0.80, 1.43)
Smoking status						
Non-smoker	393/732 (53.7%)	Reference	Reference	366/626 (58.5%)	Reference	Reference
Current smoker	131/279 (47.0%)	0.87 (0.77, 1.00)	0.99 (0.84, 1.16)	136/220 (61.8%)	1.06 (0.92, 1.22)	1.12 (0.95, 1.33)
Alcohol use						
Does not use alcohol	309/593 (52.1%)	Reference	Reference	318/528 (60.2%)	Reference	Reference
Uses alcohol	215/418 (51.4%)	0.99 (0.90, 1.08)	1.06 (0.98, 1.16)	184/318 (57.9%)	0.96 (0.82, 1.12)	0.93 (0.81, 1.07)
Transportation to clinic						
On foot	335/661 (50.7%)	Reference	Reference	309/547 (56.5%)	Reference	Reference
Minibus taxi or other	189/350 (54.0%)	1.07 (0.90, 1.26)	1.02 (0.87, 1.20)	193/299 (64.6%)	1.14 (1.01, 1.30)	1.08 (0.93, 1.25)
Travel time to clinic						
≤15 minutes	174/359 (48.5%)	Reference	Reference	152/256 (59.4%)	Reference	Reference
16-30 minutes	243/443 (54.9%)	1.13 (0.97, 1.32)	1.15 (0.98, 1.34)	247/389 (63.5%)	1.07 (0.91, 1.26)	1.08 (0.91, 1.27)
>30 minutes	107/209 (51.2%)	1.06 (0.83, 1.34)	1.08 (0.85, 1.37)	103/201 (51.2%)	0.86 (0.68, 1.09)	0.89 (0.69, 1.14)

Table 3.3. Unadjusted and adjusted estimates of 90-day ART uptake, stratified by period of enrollment

	Pre-UTT Cohort (n=1,010)			UTT Cohort (n=827)		
Characteristic	ART uptake/n (%)	RR (95% CI)	aRR (95% CI)	ART uptake/n (%)	RR (95% CI)	aRR (95% CI)
CD4 count (cells/mm^3)						
≤50	54/81 (66.7%)	0.97 (0.84, 1.13)	0.93 (0.78, 1.10)	44/57 (77.2%)	1.09 (0.91, 1.32)	1.14 (0.96, 1.36)
51-200	238/348 (68.4%)	Reference	Reference	141/200 (70.5%)	Reference	Reference
201-350	186/314 (59.2%)	0.87 (0.79, 0.95)	0.86 (0.78, 0.94)	138/203 (68.0%)	0.96 (0.82, 1.13)	0.98 (0.83, 1.15)
351-500	154/267 (57.7%)	0.84 (0.73, 0.97)	0.82 (0.71, 0.95)	107/165 (64.9%)	0.92 (0.78, 1.09)	0.93 (0.78, 1.10)
>500	--	--	--	139/202 (68.8%)	0.98 (0.85, 1.12)	1.00 (0.85, 1.17)
Sex						
Male	242/438 (55.3%)	Reference	Reference	227/326 (69.6%)	Reference	Reference
Female	390/572 (68.2%)	1.23 (1.08, 1.41)	1.24 (1.04, 1.48)	342/501 (68.3%)	0.98 (0.90, 1.07)	1.02 (0.90, 1.16)
Age (years)						
18-24	95/149 (63.8%)	Reference	Reference	82/127 (64.6%)	Reference	Reference
25-34	239/392 (61.0%)	0.96 (0.85, 1.07)	0.97 (0.86, 1.10)	212/314 (67.5%)	1.05 (0.91, 1.21)	1.03 (0.89, 1.20)
35-44	180/298 (60.4%)	0.95 (0.80, 1.12)	0.96 (0.78, 1.18)	156/222 (70.3%)	1.09 (0.93, 1.27)	1.07 (0.90, 1.26)
≥45	118/171 (69.0%)	1.08 (0.90, 1.31)	1.07 (0.87, 1.32)	119/164 (72.6%)	1.12 (0.97, 1.31)	1.10 (0.94, 1.29)
Previous TB diagnosis						
No	559/899 (62.2%)	Reference	Reference	517/755 (68.5%)	Reference	Reference
Yes	73/111 (65.8%)	1.06 (0.95, 1.18)	1.08 (0.95, 1.23)	52/72 (72.2%)	1.05 (0.92, 1.21)	1.04 (0.90, 1.20)
Education level						
Grade 0-5 or less	98/152 (64.5%)	Reference	Reference	77/106 (72.6%)	Reference	Reference
Grade 6-11	376/624 (60.3%)	0.93 (0.83, 1.05)	0.96 (0.84, 1.10)	336/505 (66.5%)	0.92 (0.80, 1.05)	0.92 (0.78, 1.09)
Grade 12 or higher	158/234 (67.5%)	1.05 (0.91, 1.21)	1.08 (0.90, 1.30)	156/216 (72.2%)	0.99 (0.85, 1.16)	0.98 (0.81, 1.19)
Employment status						
Unemployed	330/522 (63.2%)	Reference	Reference	306/457 (67.0%)	Reference	Reference
Employed	302/488 (61.9%)	0.98 (0.91, 1.06)	1.05 (0.96, 1.14)	263/370 (71.1%)	1.06 (0.98, 1.15)	0.96 (0.88, 1.06)

Total family income per month (ZAR)						
<1,000	200/320 (62.5%)	Reference	Reference	166/281 (59.1%)	Reference	Reference
1,000-5,000	348/567 (61.4%)	0.98 (0.86, 1.12)	0.99 (0.86, 1.13)	307/430 (71.4%)	1.21 (1.06, 1.37)	1.20 (1.06, 1.37)
>5,000	84/123 (68.3%)	1.09 (0.92, 1.30)	1.07 (0.88, 1.32)	96/116 (82.8%)	1.40 (1.20, 1.63)	1.39 (1.18, 1.64)
Household size (including respondent)						
1 person	70/121 (57.9%)	Reference	Reference	55/86 (64.0%)	Reference	Reference
2 people	113/176 (64.2%)	1.11 (0.92, 1.34)	1.07 (0.90, 1.28)	133/181 (73.5%)	1.15 (0.96, 1.38)	1.18 (0.99, 1.41)
3-5 people	326/509 (64.1%)	1.11 (0.91, 1.35)	1.07 (0.89, 1.28)	264/396 (66.7%)	1.04 (0.87, 1.24)	1.08 (0.91, 1.29)
≥6 people	123/204 (60.3%)	1.04 (0.86, 1.26)	0.99 (0.83, 1.17)	117/164 (71.3%)	1.12 (0.94, 1.32)	1.15 (0.95, 1.39)
Smoking status						
Non-smoker	478/731 (65.4%)	Reference	Reference	419/611 (68.6%)	Reference	Reference
Current smoker	154/279 (55.2%)	0.84 (0.77, 0.92)	0.98 (0.88, 1.09)	150/216 (69.4%)	1.01 (0.91, 1.13)	1.04 (0.91, 1.19)
Alcohol use						
Does not use alcohol	386/592 (65.2%)	Reference	Reference	356/515 (69.1%)	Reference	Reference
Uses alcohol	246/418 (58.9%)	0.90 (0.84, 0.97)	0.97 (0.89, 1.07)	213/312 (68.3%)	0.99 (0.87, 1.13)	0.99 (0.89, 1.09)
Transportation to clinic						
On foot	406/660 (61.5%)	Reference	Reference	352/538 (65.4%)	Reference	Reference
Minibus taxi or other	226/350 (64.6%)	1.05 (0.92, 1.20)	1.01 (0.89, 1.15)	217/289 (75.1%)	1.15 (1.02, 1.29)	1.07 (0.93, 1.22)
Travel time to clinic						
≤15 minutes	211/358 (58.9%)	Reference	Reference	177/254 (69.7%)	Reference	Reference
16-30 minutes	291/443 (65.7%)	1.11 (0.96, 1.29)	1.13 (0.97, 1.31)	275/381 (72.2%)	1.04 (0.89, 1.20)	1.05 (0.89, 1.24)
>30 minutes	130/209 (62.2%)	1.06 (0.91, 1.23)	1.09 (0.94, 1.26)	117/192 (60.9%)	0.87 (0.73, 1.05)	0.90 (0.73, 1.11)

Appendix Table 3.1. Characteristics of 2,365 men and non-pregnant women newly diagnosed with HIV without active TB disease in 14 public sector healthcare facilities in North West Province, South Africa, January 2015 – May 2017

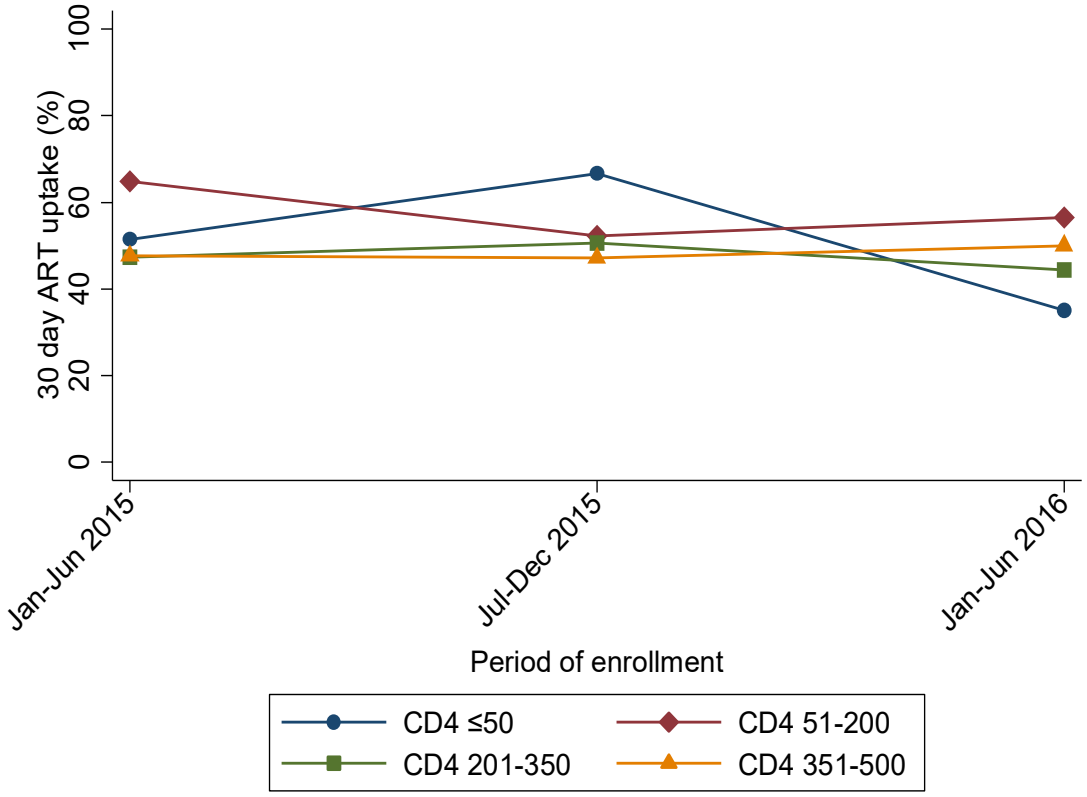
	Total n (%)	CD4 unknown n (%)	CD4 ≤50 n (%)	CD4 51-200 n (%)	CD4 201-350 n (%)	CD4 351-500 n (%)	CD4 >500 n (%)
Total	2365	94	145	576	543	451	556
Cohort							
Pre-UTT	1477 (62%)	62 (66%)	85 (59%)	368 (64%)	333 (61%)	281 (62%)	348 (63%)
UTT	888 (38%)	32 (34%)	60 (41%)	208 (36%)	210 (39%)	170 (38%)	208 (37%)
Sex and pregnancy							
Male	947 (40%)	37 (39%)	70 (48%)	259 (45%)	240 (44%)	173 (38%)	168 (30%)
Female[1]	1418 (60%)	57 (61%)	75 (52%)	317 (55%)	303 (56%)	278 (62%)	388 (70%)
Age (years)							
Median (IQR)	33 (27-41)	31 (25-38)	37 (31-45)	35 (30-42)	33 (27-42)	31 (25-40)	31 (25-39)
18-24	387 (16%)	20 (21%)	8 (6%)	51 (9%)	76 (14%)	100 (22%)	132 (24%)
25-34	914 (39%)	41 (44%)	50 (34%)	211 (7%)	212 (39%)	182 (40%)	218 (39%)
35-44	637 (27%)	20 (21%)	46 (32%)	198 (34%)	156 (29%)	99 (22%)	118 (21%)
≥45	427 (18%)	13 (14%)	41 (28%)	116 (20%)	99 (18%)	70 (16%)	88 (16%)
Previous TB diagnosis							
No	2130 (90%)	80 (85%)	122 (84%)	502 (87%)	500 (92%)	407 (90%)	519 (93%)
Yes	235 (10%)	14 (15%)	23 (16%)	74 (13%)	43 (8%)	44 (10%)	37 (7%)
Education level							
Missing	3 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (0%)	0 (0%)	0 (0%)
Grade 0-5 or less	346 (15%)	12 (13%)	21 (14%)	97 (17%)	95 (18%)	48 (11%)	73 (13%)
Grade 6-11	1444 (61%)	57 (61%)	88 (61%)	356 (62%)	332 (61%)	286 (63%)	325 (58%)
Grade 12 or higher	572 (24%)	24 (26%)	36 (25%)	123 (21%)	114 (21%)	117 (26%)	158 (28%)

Employment status							
Missing	5 (0%)	0 (0%)	1 (1%)	3 (1%)	0 (0%)	1 (0%)	0 (0%)
Unemployed[2]	1282 (54%)	49 (52%)	74 (51%)	296 (51%)	295 (54%)	241 (53%)	327 (59%)
Employed	1078 (46%)	45 (48%)	70 (48%)	277 (48%)	248 (46%)	209 (46%)	229 (41%)
Total family income per month (ZAR)[3]							
Missing	27 (1%)	1 (1%)	2 (1%)	6 (1%)	10 (2%)	5 (1%)	3 (1%)
<1,000	777 (33%)	30 (32%)	49 (34%)	186 (32%)	176 (32%)	144 (32%)	192 (35%)
1,000-5,000	1265 (54%)	50 (53%)	76 (52%)	303 (53%)	300 (55%)	246 (55%)	290 (52%)
>5,000	296 (13%)	13 (14%)	18 (12%)	81 (14%)	57 (11%)	56 (12%)	71 (13%)
Household size (including respondent)							
Missing	5 (0%)	0 (0%)	1 (1%)	1 (0%)	1 (0%)	0 (0%)	2 (0%)
1 person	263 (11%)	9 (10%)	26 (18%)	77 (13%)	66 (12%)	34 (8%)	51 (9%)
2 people	468 (20%)	21 (22%)	23 (16%)	113 (20%)	110 (20%)	86 (19%)	115 (21%)
3-5 people	1155 (49%)	51 (54%)	72 (50%)	274 (48%)	249 (46%)	230 (51%)	279 (50%)
≥6 people	474 (20%)	13 (14%)	23 (16%)	111 (19%)	117 (22%)	101 (22%)	109 (20%)
Smoking status							
Missing	7 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)	2 (0%)	3 (1%)
Non-smoker[4]	1721 (73%)	69 (73%)	116 (80%)	432 (75%)	388 (71%)	322 (72%)	394 (71%)
Current smoker[5]	637 (27%)	25 (27%)	29 (20%)	143 (25%)	154 (28%)	127 (28%)	159 (29%)
Alcohol use							
Missing	7 (0%)	0 (0%)	1 (1%)	2 (0%)	1 (0%)	2 (0%)	1 (0%)
Does not use alcohol	1402 (59%)	57 (61%)	104 (72%)	344 (60%)	328 (60%)	260 (58%)	309 (56%)
Uses alcohol	956 (40%)	37 (39%)	40 (28%)	230 (40%)	214 (39%)	189 (42%)	246 (44%)
Transportation to clinic							
Missing	15 (1%)	0 (0%)	0 (0%)	6 (1%)	4 (1%)	2 (0%)	3 (1%)
On foot	1554 (66%)	53 (56%)	83 (57%)	345 (60%)	354 (65%)	314 (70%)	405 (73%)
Minibus taxi or other[6]	796 (34%)	41 (44%)	62 (43%)	225 (39%)	185 (34%)	135 (30%)	148 (27%)
Travel time to clinic							
Missing	21 (1%)	1 (1%)	0 (0%)	6 (1%)	4 (1%)	5 (1%)	5 (1%)

≤15 minutes	767 (32%)	25 (27%)	53 (37%)	211 (37%)	181 (33%)	129 (29%)	168 (30%)
16-30 minutes	1047 (44%)	47 (50%)	65 (45%)	231 (40%)	242 (45%)	214 (48%)	248 (45%)
>30 minutes	530 (22%)	21 (22%)	27 (19%)	128 (22%)	116 (21%)	103 (23%)	135 (24%)

[1]Includes 89 women with unknown or missing pregnancy status
[2]Includes 76 students and 11 who reported 'other', including: 3 who reported receiving grants, 1 who reported a learnership, 6 pensioners, and 1 who did voluntary work
[3]Note 1 USD = 15.319 ZAR in 2016 (https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates)
[4]Includes 64 former smokers and 1657 never smokers
[5]Includes 533 daily smokers and 104 who smoke less than daily
[6]Includes 166 PLHIV who reported other forms of transportation: 26 who reported using a bicycle, 128 who reported a car or motorcycle, 6 who reported "tambai", 5 who reported NGO-provided or work-provided transport, and 1 who reported using a wheelchair

Appendix Figure 3.1. 30-day ART initiation in the pre-UTT era at 3 time points, stratified by baseline CD4 count



Chapter IV: Challenges in the implementation of isoniazid preventive therapy: low utilization of TST and high clinic-level variability in provision of isoniazid preventive therapy to newly diagnosed people living with HIV in South Africa

Abstract

Background: Isoniazid preventive therapy (IPT) reduces the risk of tuberculosis among people living with HIV (PLHIV). We sought to describe IPT provision to PLHIV and predictors of IPT initiation in South Africa.

Methods: We included newly diagnosed, adult (≥18), PLHIV, enrolled between January 2015-May 2017 at 7 public-sector clinics in North West province. We present IPT provision as simple proportions before and after implementation of the universal test and treat (UTT) guidelines for HIV infection, by clinic, and by ART initiation (never, ≤30 or >30 days after HIV diagnosis). We evaluated predictors of IPT initiation among participants who initiated ART ≤30 days using multi-level Poisson regression with robust standard errors. Results are presented as prevalence ratios (PR) and 95% confidence intervals (CI).

Results: Of 1,184 PLHIV included, 24% started IPT, with no difference observed before and after UTT. IPT provision varied across clinics (6%-45%). Few participants who never started ART were prescribed IPT (2%) while no difference was observed among those who started ART ≤30 (33%) or >30 (36%) days. Among participants who started ART ≤30 days, TST was used infrequently but was associated with IPT provision (PR: 2.90; 95% CI: 1.68, 5.00) while pregnant women (PR: 0.67; 95% CI: 0.49, 0.94) were less likely to be prescribed IPT than non-pregnant women.

Conclusions: IPT provision was low before and after UTT, with variability by clinic. Few patient-level characteristics were associated with IPT initiation.

Interventions to improve prescribing practices by healthcare providers may be needed to increase IPT use.

Introduction

South Africa has one of the world's highest incidence rates of tuberculosis (TB), estimated at 567 cases per 100,000 individuals in 2017.[1] TB is the leading natural cause of death nationally, accounting for 11.2% of deaths in 15-44 year-olds in 2016.[2] South Africa is also home to the world's largest population of people living with HIV (PLHIV), estimated at 7.4 million individuals.[3] HIV is the primary risk factor for TB disease in South Africa and 60% of TB cases are HIV co-infected.[1] Antiretroviral therapy (ART) use reduces the risk of incident TB by approximately 65% in PLHIV, with greater reductions at lower CD4 counts.[4] A further risk reduction of more than 30% can be achieved with provision of isoniazid preventive therapy (IPT) in combination with ART, primarily among PLHIV with latent TB infection (LTBI).[5,6] In South Africa, the prevalence of LTBI among people living in high-density townships ranges from 34-45% overall, with estimates as high as 88% in HIV-negative 31-35 year olds.[7,8]

Using a mathematical model, it was estimated that 12 months of IPT to 85% of PLHIV starting ART in a high-burden setting in South Africa could reduce TB incidence by more than 20% in those patients compared to no IPT use.[9] With expanded ART coverage as a result of South Africa's shift to universal test and treat for HIV infection, anticipated reductions in TB incidence were even greater.[9] However, despite evidence that IPT is an effective strategy for reducing TB incidence, uptake has historically been below global and national targets in South Africa. In 2017, just 53% of PLHIV newly enrolled in HIV care were started on

IPT, far short of the goal of >90% by 2021 laid out in South Africa's National Strategic Plan for HIV, TB and STIs 2017-2021.[1,10]

The South African National Department of Health (NDoH) 2015 HIV treatment guidelines recommended varying durations of IPT for PLHIV of 6-36 months based on the result of a tuberculin skin test (TST) and eligibility for ART.[11] However, TST is a challenging test to implement in routine care. It requires skilled healthcare workers knowledgeable in placement and reading of results and a visit by the patient within 48 to 72 hours of placement to have the result read, which has contributed to its under-utilization. Several other barriers to IPT provision have been identified, including a lack of patient and provider awareness of IPT benefits, the need to rule out TB disease prior to IPT initiation and, in conjunction, fears of causing INH mono-resistance due to inappropriate use of IPT in patients with unrecognized TB.[12,13]

In light of these challenges, understanding who, if anyone, healthcare providers are prioritizing for IPT initiation is important for the design of future interventions to increase provision. In addition, patients not yet eligible for ART initiation are often lost from HIV care[14] and, as a result, are less likely to initiate IPT despite being eligible to do so. Given that the expansion of South Africa's national HIV treatment guidelines in 2016 removed HIV treatment eligibility requirements,[15] increases in ART uptake may result in concurrent increases in IPT provision. Thus, in this analysis we sought to: (1) describe changes in IPT provision to newly diagnosed PLHIV before and after the implementation of the

2016 HIV treatment guidelines, (2) describe variability in clinic-level provision of IPT, and (3) identify predictors of IPT initiation among PLHIV on ART.

Methods

Study sites

We conducted a cluster randomized trial (TEKO) to evaluate the QuantiFERON-TB Gold In-Tube (QGIT) test, an interferon-γ release assay, against the standard of care TST for the diagnosis of LTBI and uptake of IPT. Participants were enrolled at 14 public-sector facilities in the Dr. Kenneth Kaunda District of North West province, South Africa. Data for the current analysis was obtained from the 7 standard of care sites participating in the TEKO trial to understand IPT provision under routine conditions.

HIV prevalence in the Dr. Kenneth Kaunda District is estimated at 12.9%.[16] TB incidence was estimated as 690 cases per 100,000 individuals in 2015 and approximately 64% of TB cases were HIV co-infected in that year.[17] Treatment for HIV and TB are provided according to NDoH guidelines and this analysis covered the 2015 and 2016 HIV guidelines. Under the 2015 guidelines, in place from January 2015 to August 2016, HIV treatment was provided to the following individuals: those with a WHO stage 3 or 4 comorbidity, TB disease, or hepatitis B co-infection, pregnant and breastfeeding women, and PLHIV with a CD4 count ≤500 cells/mm^3.[11] From September 2016, all PLHIV were eligible to initiate ART.[15]

The 2015 guidelines also made recommendations for IPT provision. All PLHIV on ART without symptoms of TB disease were recommended to receive IPT, with the duration dependent on the TST result, while PLHIV not yet on ART (i.e., those with a CD4 >500 cells/mm^3) were not recommended to receive IPT if they had a negative TST (Table 4.1).[11] No IPT was recommended in patients for whom TB was suspected. Instead, TB disease should be investigated and, if ruled out, IPT eligibility should be re-assessed 3 months later. Likewise, patients with a prior TB diagnosis were only recommended to receive IPT if there was proof of bacteriological cure. In the absence of such proof, IPT eligibility should be re-assessed after 3 months.[11]

Study population

Patients were eligible to be enrolled in TEKO if they were ≥18 years old, newly diagnosed with HIV (defined as diagnosis within 30 days of study enrollment), and did not have TB disease. Patients who were not eligible for IPT initiation due to excessive alcohol use or peripheral neuropathy were excluded during screening. Enrolled participants across all 14 clinics were excluded from the analytic dataset for the following reasons: not newly diagnosed with HIV, defined as a clinic visit, CD4 count, or viral load recorded more than 30 days prior to study enrollment or suppressed (<400 copies/mL) baseline viral load (prior to or within 7 days of either study enrollment or ART initiation) (n=331); prevalent TB (n=64); no age recorded (n=5); ART or IPT start date prior to the earliest of study enrollment or first CD4 count date (n=25); or no evidence that a file was ever attempted to be found (n=30). For this analysis, we included eligible

study participants enrolled at the 7 standard of care sites between January 2015-May 2017.

During screening and enrollment, participants were interviewed by a study staff member. Data collected during this process and used in this analysis included sex and pregnancy status, age, previous TB diagnoses, smoking status, and alcohol use. Participants were then followed via their medical records for a maximum of two years post-study enrollment to obtain information on TST results, TB symptoms, laboratory test results, and the dates of ART and IPT initiation. Data were collected from paper and electronic files, including Tier.Net, South Africa's electronic HIV registry, and the South African National Health Laboratory Service. Follow up data abstraction was completed in May 2018. Data were collected using REDCap (Research Electronic Data Capture) hosted at Johns Hopkins University.[18]

Variable definitions

We defined a proxy for the date of HIV diagnosis ("first known date") as the earliest of study enrollment or the first CD4 count date, for which blood is typically drawn on the same day as diagnosis. Participants whose first known date was between January 2015-June 2016 were included in the pre-universal test and treat (UTT) cohort while those enrolled between September 2016-May 2017 were included in the UTT cohort. A break in enrollment occurred in July and August 2016, during which time re-training of clinic staff on interpretation and use of QGIT results to inform IPT provision took place.

Participants whose files were attempted to be found but who never returned to the clinic were assumed to have not started ART or IPT. Those for whom files were found were categorized as never starting ART or starting ART ≤30 days or >30 days after the first known date, irrespective of ART eligibility at HIV diagnosis. For participants deemed both ART and IPT eligible, guidelines recommended initiation of ART first followed by IPT when stable on ART. For pregnant women, in particular, guidelines stated that ART should be started first, with IPT started after a minimum of 1 month on ART. Thus, we defined IPT initiation as occurring within 180 days of the ART initiation date while also allowing for IPT to be initiated prior to ART initiation, as sometimes happens under routine care. For participants who never started ART, we defined IPT initiation as occurring within 180 days of the first known date. Participants for whom data abstraction was completed prior to 180 days after the first known date (for those who did not start ART) or ART initiation were excluded from analyses (Figure 4.1).

Potential predictors of interest for IPT initiation among those who started ART within 30 days included: sex and pregnancy status at enrollment (male, non-pregnant female, or pregnant female), age at enrollment (categorized as 18-24, 25-34, 35-44, and ≥45), baseline CD4 count (defined as the first CD4 count conducted between 30 days prior to 30 days after study enrollment and categorized as ≤50, 51-200, 201-350, 351-500, and >500 cells/mm^3), previous TB diagnosis (yes or no), smoking status (non-smoker or former smoker versus current smoker), and alcohol use (yes or no). We also considered indicators for

IPT eligibility and duration, including any TB symptoms (cough, fever, night sweats or weight loss, categorized as not recorded, no symptoms, or at least 1 symptom), and whether or not a TST was placed. The presence of TB symptoms was defined based on the earliest recorded symptom screen up to the date of IPT initiation or, for participants who did not start IPT, up to 180 days after the ART initiation date. Guidelines in place during the study indicated that IPT could be started without a TST result but a TST should be conducted within one month of starting IPT. Thus, we defined TST placement as a TST done up to 30 days after the IPT start date or, for participants who did not start IPT, up to 180 days after the ART initiation date. While TST results are presented in the table of baseline demographic and clinical characteristics, the number of participants with a TST was small, and even fewer had a result recorded. Thus, we included TST as a dichotomous variable (placed/not placed) in the regression analysis.

Statistical analysis

For the first objective, we describe the impact of UTT on IPT provision and present simple proportions stratified by ART use (none, started ≤30 days, started >30 days) among all participants included in the analytic dataset. Likewise, for the second objective we describe clinic-level variability in IPT provision and present simple proportions for all study participants and for those who initiated ART within 30 days, pre- and post-UTT implementation. For the third objective, we evaluate predictors of IPT initiation. We restricted the population to only those individuals who initiated ART within 30 days as all PLHIV in South Africa are now eligible for same-day ART initiation.[19] With shorter timelines to ART initiation, this

study population is more relevant to current conditions. We then conducted a complete case analysis using multilevel Poisson regression with robust standard errors to evaluate the association between IPT initiation and the predictors of interest (as defined above), including a random effect term for the clinic in which a participant was enrolled to account for clustering. Results are presented as prevalence ratios (PR) with 95% confidence intervals (CI).

Ethical approval

Ethical approval was obtained from the Institutional Review Board of the Johns Hopkins University School of Medicine and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.

Results

Across the 7 standard of care sites, 1,184 newly diagnosed PLHIV were enrolled between January 2015-May 2017 and were included in this analysis (Figure 4.1). Approximately 29% (n=345) of participants never started ART during the follow-up period. The remaining 839 participants started ART, 645 (77%) within 30 days of the first known date and 194 (23%) after more than 30 days. Overall, 24% of participants started IPT within 180 days of either study enrollment or ART initiation. IPT provision among participants who never started ART was low (2%) while approximately one-third of participants who initiated ART started IPT, regardless of whether they started within (33%) or after (36%) 30 days of the first known date (Figure 4.1).

IPT provision before and after the implementation of UTT for PLHIV

Comparing the pre-UTT period to the UTT period, the proportion of participants initiating IPT was similar (24% vs 25%). This reflected an increase in the overall proportion of participants who initiated ART (n=535/800 [67%] vs n=304/384 [79%]), counterbalanced by a decline in the proportion of participants who initiated IPT among those who never started ART (n=8/265 [3%] vs n=0/80 [0%]) and those who started ART within 30 days (n=132/383 [34%] vs n=80/262 [31%]). IPT initiation was stable among those who started ART after 30 days (n=54/152 [36%] vs n=15/42 [36%]) (Table 4.2).

Clinic-level variability in IPT provision

There was substantial variability in IPT provision by clinic. In the pre-UTT period, provision ranged from 8% to 45%. In the UTT period, we observed increases in provision at some clinics while also observing substantial declines in others. It was again highly variable, ranging from 4% to 47% (Figure 4.2a). As IPT provision was higher among participants who initiated ART, we also evaluated variability in ART initiation by clinic. In the pre-UTT period, any ART initiation ranged from 58% to 73% (25% to 54% for ART ≤30 days) and in the UTT period, from 68% to 86% (47% to 83% for ART ≤30 days) (Figure 4.2a). When restricted to participants who initiated ART within 30 days, IPT provision ranged from 9% to 67% in the pre-UTT period and from 6% to 60% in the UTT period. A substantial decline in IPT provision from 48% pre-UTT to 10% in the UTT period was observed at one facility; however, few individuals enrolled and initiated ART within 30 days in the UTT period at that clinic (n=10/14 [71%]) (Figure 4.2b).

Predictors of IPT initiation among PLHIV who started ART

Six hundred and forty-five participants started ART within 30 days of HIV diagnosis and 620 (96%) had complete data on all predictors of interest. The median (interquartile range [IQR]) age of included participants was 32 years (26-39), 45% were non-pregnant women, and 33% were diagnosed with a CD4 count ≤200 cells/mm^3. In total, 207 (33%) started IPT. Pregnant women (PR: 0.67; 95% CI: 0.49, 0.94) and men (PR: 0.86; 95% CI: 0.69, 1.07) were less likely to start IPT than non-pregnant women. Participants with a prior TB diagnosis were approximately 30% more likely to receive IPT, though the confidence interval was wide and should be interpreted with caution (PR: 1.31; 95% CI: 0.70, 2.45). Few participants had TB symptoms recorded prior to IPT initiation (n=45) and 31% started IPT, which was similar to those without TB symptoms (34%). The median (IQR) time to IPT initiation for the 14 participants who started IPT after reporting a TB symptom was 45 days (7-63). TST was utilized infrequently and just 44 participants (7%) had a TST placed. Almost half (48%, n=21) of the TST's placed were done so at a single clinic, which amounted to 18% of participants at that facility. However, increased utilization of TST at that clinic did not result in substantially higher IPT provision within 180 days compared to other clinics (38% vs 32% for all other clinics combined). Despite this, participants who had a TST placed had almost triple the prevalence of IPT provision compared to participants who did not receive a TST (PR: 2.90; 95% CI: 1.68, 5.00) (Table 4.3).

Discussion

Following the lead of the World Health Organization, South Africa has set ambitious targets for TB preventive therapy uptake to reduce TB incidence, aiming to reach at least 90% of PLHIV on ART by 2021.[10] However, our results showed that just 24% of all participants and 33% of those on ART started IPT within 180 days, with substantial variability by clinic, far below both the target level and the national average of 53% reported in 2017.[1] While the data utilized for this analysis was collected as part of a cluster randomized trial, we only included standard of care clinics which were following NDoH guidelines for ART and IPT provision. Thus, our findings indicate that some facilities in high-TB burden settings are under-performing compared to national estimates.

Our results of high clinic level variability with low overall IPT provision are in line with results from other studies in South Africa. Using data collected from clinic registers, IPT provision at three clinics in Johannesburg ranged from 0.7% to 34% prior to an intervention designed to improve IPT prescribing.[12] Likewise, in a study conducted of South African patients who tested positive for HIV through home or mobile testing services and linked to a healthcare facility, IPT provision was just 18%,[20] similar to our findings of approximately 24%. No differences in IPT provision based on the presence or absence of TB symptoms were observed in that study, which is in line with our results.[20] In addition, in a medical record review of 925 IPT-eligible patients in Johannesburg, 8% (n=76) started IPT.[12] The authors observed an association between pregnancy and an increased likelihood of starting IPT,[12] in contrast to our findings that pregnant

women were less likely to be prescribed IPT than non-pregnant women. Taken together, these results highlight clinic-level differences in both IPT provision and targeting of IPT to specific patients.

South Africa updated their HIV treatment guidelines in 2016 to allow for universal ART for all PLHIV.[15] As a result of this change, we anticipated that fewer PLHIV would be lost from care between HIV diagnosis and ART initiation as all would be eligible to start ART. With reduced loss from care, we expected to observe an increase in IPT provision in line with an increase in ART initiation. While we did observe a substantial increase in ART initiation before and after the implementation of these guidelines, we did not observe an increase in IPT uptake. In the UTT era, proportionally fewer participants started IPT among those who started ART within 30 days and no participants started IPT among those who did not start ART. Of the 80 participants who did not start ART in the UTT cohort, 89% had either zero or one follow-up visit recorded after study enrollment compared to 73% of the 265 participants who did not start ART in the pre-UTT cohort. Thus, there were few opportunities for healthcare workers to evaluate these participants for IPT eligibility. The decline in IPT provision among participants who started ART within 30 days was driven by specific clinics in this study. While we can only speculate as to reasons why this decline was observed, it may reflect staff turnover, an increased burden on healthcare workers who needed to initiate a larger proportion of newly diagnosed PLHIV on ART in the UTT era, potentially increased loss from care in the UTT era, or stock outs of IPT or TST at those facilities.

Previous research has reported provider concern in prescribing IPT due to fears of causing isoniazid (INH) resistance by inappropriately providing IPT to patients with unidentified TB disease, especially given the often atypical presentation of TB in PLHIV, as a barrier to IPT implementation.[13] However, IPT has not been found to increase INH resistance in the literature.[21] Thus, allaying provider fears of INH resistance may improve IPT provision. In addition, guidelines that recommend IPT based on TST status may hinder IPT provision as TST is a difficult test to implement in practice. While the South African guidelines in place during the period of this analysis did recommend IPT be started when a TST was not done, they also stated that a TST must be done within one month of IPT initiation for patients without a TST result.[11] TST stock outs have been reported in South Africa[22] and globally[23,24] in recent years, which may have contributed to the low utilization of TST in our study clinics.

The results of our study should be viewed in light of several limitations. Given that data on TST and IPT stock outs were not available for our study clinics at the time of analysis, we are unable to evaluate the role of stock outs in our findings. Second, we did not collect information on clinic-level factors that may be associated with healthcare service delivery generally, and IPT provision specifically, that may aid in understanding the clinic-level variability we observed. Factors such as patient to provider ratio, clinic waiting times, proportion of staff trained in and conducting TST placement and reading, and availability of IPT guidelines within the facility all may influence IPT provision at the clinic level. In addition, our definition of IPT provision within 180 days may underestimate total

IPT provision if patients start IPT after a longer duration in HIV care. Finally, we identified few participants investigated for TB disease (n=13) among our study participants. While this may indicate poor adherence to guidelines to investigate TB in PLHIV reporting any TB-related symptom, it may also reflect misclassification in our study database (i.e., participants not recorded as TB suspects in our database when they were truly investigated for TB disease), or under-recording of TB investigations in medical records by healthcare providers.

Conclusion

We observed low levels of IPT provision among newly diagnosed PLHIV with wide variability by clinic. Future research should consider clinic-level factors that may be associated with IPT provision to identify opportunities for interventions to increase IPT prescribing practices.

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Table 4.1. IPT guidelines according to TST and ART status as per 2015 South African National Department of Health guidelines for treatment of HIV infection

	Pregnant and breastfeeding women[1]	**PLHIV not yet on ART**	**PLHIV on ART**
TST positive	36 months	36 months[2]	36 months
TST negative	12 months	No IPT[3]	12 months[3]
TST not available	12 months	6 months[3]	12 months[3]

[1]ART should be started first and IPT started ≥1 month later
[2]IPT should be stopped if TST later becomes negative
[3]If later TST becomes positive, IPT should be extended to 36 months

Figure 4.1. Flow chart of TEKO participants included in IPT analyses enrolled at standard of care sites stratified by ART uptake, January 2015-May 2017

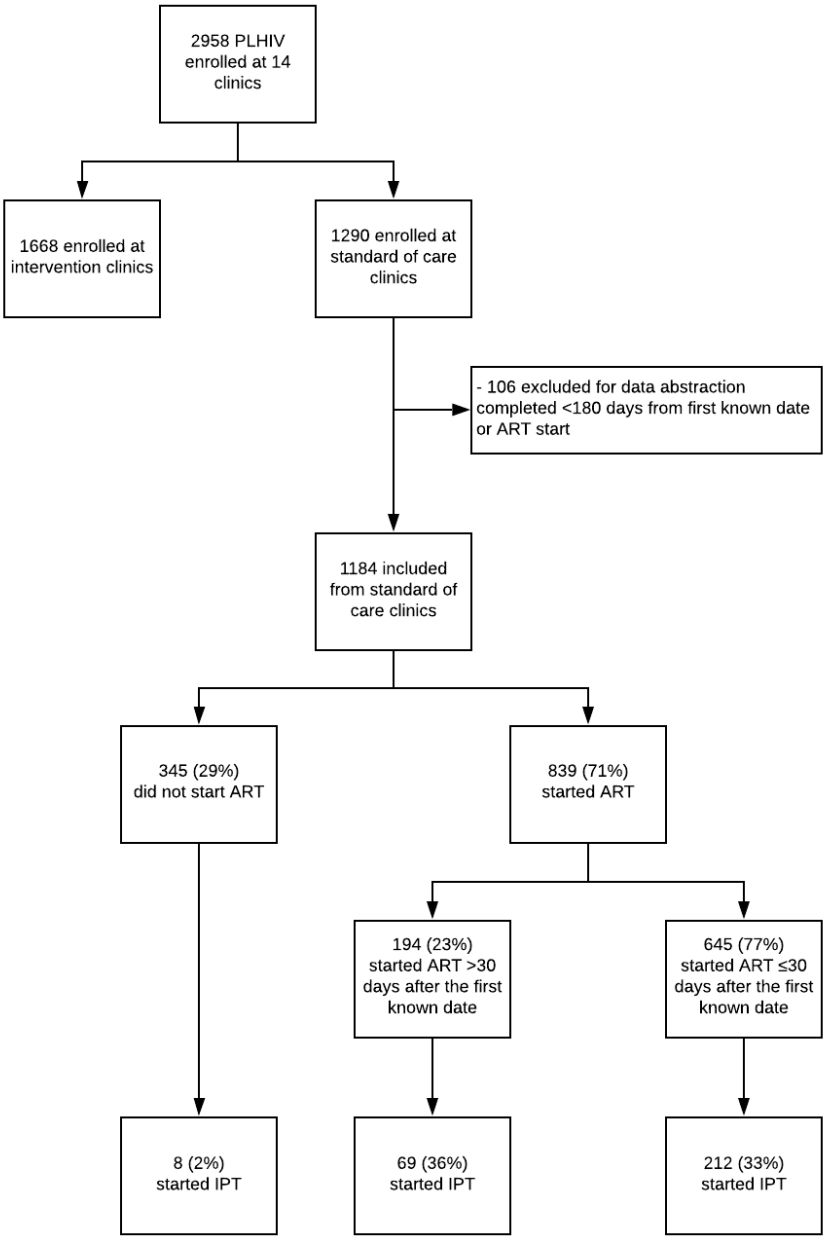

Table 4.2. ART and IPT initiation before and after implementation of the universal test and treat policy for PLHIV, stratified by timing of ART initiation

	Total n (%)	Pre-UTT n (%)	UTT n (%)
ART initiation	1184	800	384
Never started ART	345 (29%)	265 (33%)	80 (21%)
ART initiation ≤30 days	645 (54%)	383 (48%)	262 (68%)
ART initiation >30 days	194 (16%)	152 (19%)	42 (11%)
IPT initiation	289 (24%)	194 (24%)	95 (25%)
IPT initiation by ART status			
Never started ART	8/345 (2%)	8/265 (3%)	0/80 (0%)
ART initiation ≤30 days	212/645 (33%)	132/383 (34%)	80/262 (31%)
ART initiation >30 days	69/194 (36%)	54/152 (36%)	15/42 (36%)

Figure 4.2. IPT provision by clinic

Panel a depicts IPT provision to all enrolled participants at each clinic overlaid with ART initiation. Panel b depicts IPT initiation among participants who initiated ART within 30 days of the first known date. IPT initiation is stratified by cohort of enrollment (either under the pre-UTT or UTT guidelines) in both panels.

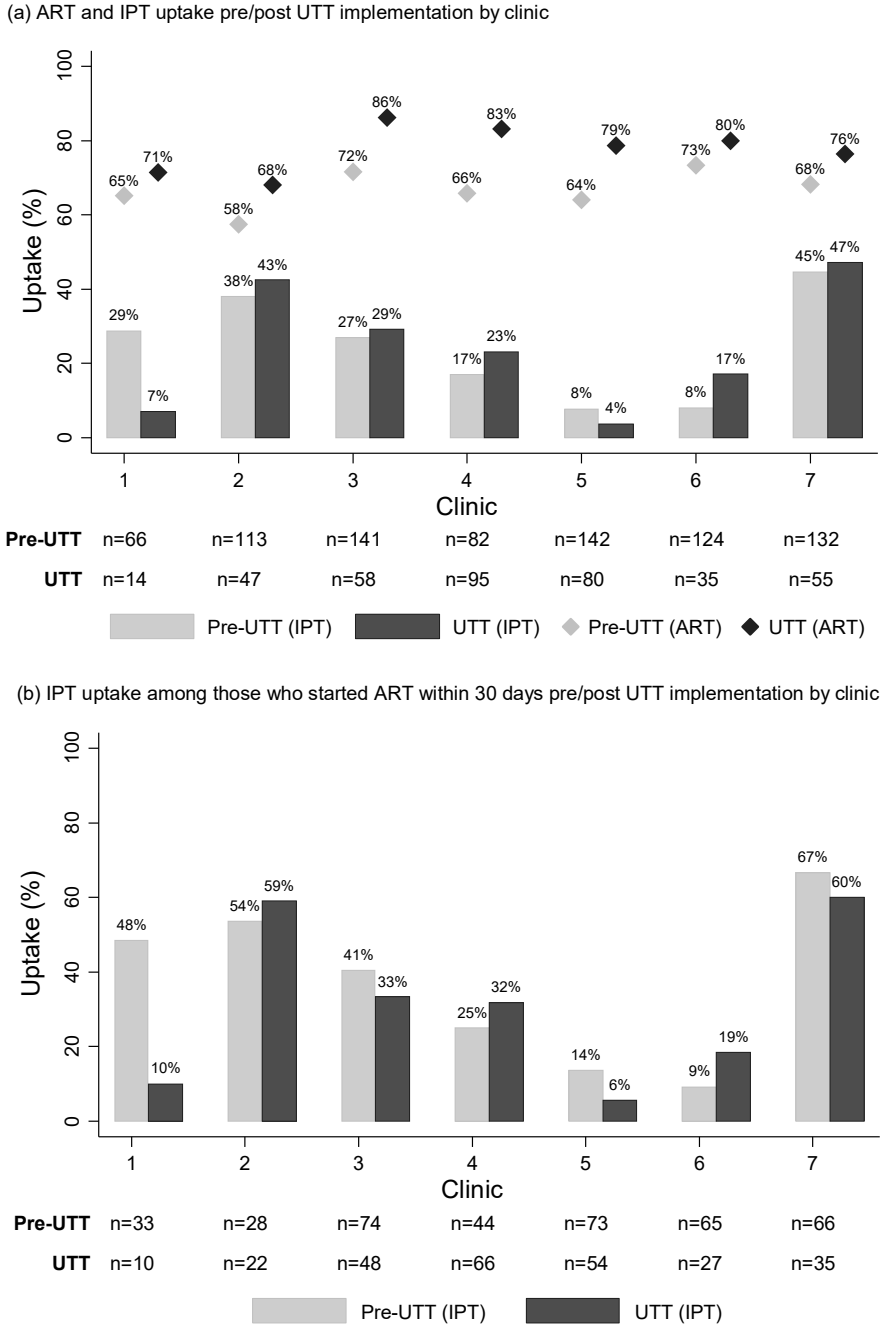

Table 4.3. Association between patient characteristics and IPT initiation among newly diagnosed PLHIV who initiated ART ≤30 days

	Total n (%)	Did not initiate IPT n (%)	Initiated IPT n (%)	Prevalence ratio (95% CI)
Total	620	413 (67%)	207 (33%)	
Sex and pregnancy				
Male	156	109 (70%)	47 (30%)	0.86 (0.69, 1.07)
Female, non-pregnant[1]	282	172 (61%)	110 (39%)	Reference
Female, pregnant	182	132 (73%)	50 (27%)	0.67 (0.49, 0.94)
Age (years)				
Median (IQR)	*32 (26-39)*	*32 (26-39)*	*31 (26-41)*	--
18-24	107	70 (65%)	37 (35%)	1.11 (0.97, 1.28)
25-34	263	177 (67%)	86 (33%)	1.01 (0.73, 1.39)
35-44	166	114 (69%)	52 (31%)	Reference
≥45	84	52 (62%)	32 (38%)	1.12 (0.83, 1.51)
Baseline CD4 count				
Median (IQR)	*290.5 (169.5-469.5)*	*282 (172-468)*	*307 (164-471)*	--
≤50	32	26 (81%)	6 (19%)	0.70 (0.19, 2.56)
51-200	174	115 (66%)	59 (34%)	Reference
201-350	167	111 (66%)	56 (34%)	0.94 (0.73, 1.22)
351-500	129	79 (61%)	50 (39%)	1.01 (0.72, 1.43)
>500	118	82 (69%)	36 (31%)	0.89 (0.56, 1.43)
Previous TB diagnosis				
No	566	383 (68%)	183 (32%)	Reference
Yes	54	30 (56%)	24 (44%)	1.31 (0.70, 2.45)
TB symptoms				
Not recorded	80	55 (69%)	25 (31%)	Reference

No symptoms	495	327 (66%)	168 (34%)	1.29 (0.58, 2.87)
≥1 symptom	45	31 (69%)	14 (31%)	1.29 (0.78, 2.14)
TST result				
TST not done	576	406 (70%)	170 (30%)	Reference
TST placed	44	7 (16%)	37 (84%)	2.90 (1.68, 5.00)
TST no result	*13*	*4 (31%)*	*9 (69%)*	--
TST positive	*7*	*1 (14%)*	*6 (86%)*	--
TST negative	*24*	*2 (8%)*	*22 (92%)*	--
Smoking status				
Non-smoker[2]	504	329 (65%)	175 (35%)	Reference
Current smoker[3]	116	84 (72%)	32 (28%)	0.95 (0.69, 1.29)
Alcohol use				
Does not use alcohol	416	278 (67%)	138 (33%)	Reference
Uses alcohol	204	135 (66%)	69 (34%)	1.26 (0.98, 1.60)

[1]Includes 21 women with unknown or missing pregnancy status
[2]Includes 15 former smokers and 489 never smokers
[3]Includes 93 daily smokers and 23 less than daily smokers

Chapter V: Conclusions

South Africa has made substantial progress towards achieving the UNAIDS 90-90-90 goals. Just over 90% of people living with HIV (PLHIV) in South Africa are estimated to be diagnosed and just under 90% of PLHIV on antiretroviral therapy (ART) are virologically suppressed at a threshold of 1,000 copies/mL.[1] However, sub-optimal levels of ART uptake continue to hamper efforts to achieve epidemic control. In response to growing evidence that earlier ART initiation reduces morbidity and mortality and prevents transmission to uninfected partners, South Africa removed the CD4-based ART-eligibility threshold in September 2016.[2] As ART reduces the risk of tuberculosis (TB), expanded ART coverage has also aided in efforts to reduce TB incidence in South Africa. However, at an estimated 567 incident cases of TB per 100,000 individuals in 2017, TB incidence remains amongst the highest in the world.[3]

This dissertation utilized data collected as part of a cluster-randomized trial (TEKO) to evaluate two approaches (an interferon-γ release assay versus standard of care tuberculin skin test [TST]) for the diagnosis of latent TB infection (LTBI) with provision of IPT at 14 sites in North West province, South Africa. The analyses presented in the preceding chapters provide insight into the impact of universal eligibility for ART on timing of HIV diagnosis (using CD4 count as a proxy measure), ART uptake, and provision of IPT in newly diagnosed PLHIV.

Key findings

Prior to the implementation of the universal test and treat (UTT) guidelines, PLHIV diagnosed with a CD4 count >500 cells/mm^3 were only eligible to initiate ART if they had a World Health Organization (WHO) Stage 3 or 4

disease, active TB disease, were pregnant or breastfeeding, or had hepatitis B co-infection.[4] Given those guidelines, in aim 1 we observed that just 7% of non-pregnant PLHIV without active TB disease diagnosed with a CD4 count >500 cells/mm^3 initiated treatment in the pre-UTT era. In the UTT era, ART initiation in this patient population increased to 61%. We also observed a 7% increase in ART initiation among PLHIV diagnosed with a CD4 count ≤500 cells/mm^3, from approximately 52% in the pre-UTT era to 59% under UTT. Thus, we estimated that the implementation of UTT resulted in a 47% (95% CI: 35%, 59%) increase in ART uptake for newly eligible PLHIV compared to always eligible PLHIV.

Previous research has shown that despite widespread availability of HIV testing and treatment services in South Africa, PLHIV are still often diagnosed late in the course of infection.[5] Both quantitative and qualitative research has also raised concerns that PLHIV who are diagnosed at higher CD4 counts may be less likely to start treatment than their sicker peers.[6–9] In aim 2, we observed a median (IQR) CD4 count at HIV diagnosis of 315.5 cells/mm^3 (168-496) with no change in timing of HIV diagnosis between the pre-UTT and UTT periods. We also observed that approximately 30% of study participants were diagnosed with advanced HIV disease (CD4 count <200 cells/mm^3) and men were diagnosed with lower CD4 counts than women (median: 282 cells/mm^3 vs 340 cells/mm^3). Given the removal of the CD4-based ART eligibility threshold in the UTT period, we observed a clinically significant increase in median CD4 count at ART initiation from 222 cells/mm^3 to 309 cells/mm^3 (adjusted difference: 92.9 cells/mm^3; 95% CI: 54.0, 131.8). In analyses of the association between CD4

count stratum and ART initiation, we observed that patients diagnosed with a CD4 count >200 cells/mm^3 in the pre-UTT era were approximately 20% less likely to initiate ART within 30 days than those diagnosed with a CD4 between 51-200 cells/mm^3. However, in the UTT era, this association no longer held and 30-day ART uptake was similar across all CD4 count strata.

South Africa has set ambitious targets for IPT uptake among PLHIV, aiming to reach >90% of PLHIV by 2021.[10] However, in 2017, national estimates of IPT uptake were just 53% and previous research has indicated that uptake may be even lower than reported national estimates.[3,11] In aim 3, we observed that 24% of study participants enrolled in the 7 standard of care sites in the TEKO study initiated IPT within 180 days of either study enrollment or ART initiation. IPT uptake was higher among participants who started ART (33%) compared to those who never started (2%). We observed no change in overall IPT provision before and after implementation of UTT, though IPT provision was highly variable by clinic. We identified few patient characteristics associated with IPT provision. In a multilevel model with a random effect term for clinic, we observed that pregnant women were less likely to receive IPT than non-pregnant women (prevalence ratio [PR]: 0.67; 95% CI: 0.49, 0.94). The TST, which was recommended for establishing the duration of IPT, was used infrequently and almost half (48%) of the 44 participants who had a TST placed were seen at a single clinic. However, having a TST placed showed clear intent for IPT initiation as participants with a TST placed were almost three times as likely to receive IPT as participants who did not have a TST (PR: 2.90; 95% CI: 1.68, 5.00).

Public health implications and areas for future research

Taken together, the findings from aims 1 and 2 demonstrate that implementation of UTT has resulted in similar rates of ART initiation, regardless of health status at diagnosis. In addition, given universal ART eligibility, the median CD4 count at ART initiation is increasing which will result in larger, healthier patient populations in ART clinics. Despite this, our findings of approximately 59% 30-day ART uptake in the UTT era falls short of UNAIDS targets. However, in September 2017, the South African National Department of Health recommended same-day ART initiation for newly diagnosed PLHIV.[12] This recommendation will likely result in much greater uptake of ART than was observed in our study. As clinics populations grow, decongestion strategies that encourage off-site ART pick-up among stable patients will be important to reduce patient volume on a day-to-day basis and to ensure that healthcare providers are able to focus on the sickest patients.

Future research should evaluate HIV testing and ART uptake under these most recent changes to national guidelines. Identifying reasons for testing, especially among asymptomatic individuals, and treatment refusal in the context of universal ART eligibility and same-day ART initiation will be important for understanding whether willingness to initiate ART differs based on an individuals' underlying motivation for testing. Understanding this interplay may assist in creating interventions to assist patients who initially refuse treatment to engage in HIV care. Likewise, ongoing evaluation of long-term retention in care will be critical. PLHIV diagnosed with high CD4 counts are more likely to be

asymptomatic than those diagnosed later in the course of infection. Thus, they will likely not experience major personal health benefits after starting ART that are common among patients who initiate with advanced HIV disease. It may, therefore, be more difficult to retain patients who start ART with high CD4 counts in care if they do not experience physical benefits of treatment and innovative interventions may also be needed for retention strategies.

IPT use can greatly reduce the risk of TB disease among PLHIV and is an important component of South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022.[10] Our results in aim 3 showed that overall IPT provision is low but highly variable by clinic. We were also unable to demonstrate specific targeting of patients for IPT provision by healthcare providers. Qualitative research among healthcare providers has identified a number of barriers to IPT provision, including fears of generating isoniazid mono-resistance, the need to rule out active TB disease, and challenges associated with TST.[13,14] Continued education of healthcare providers on TB symptom screening and investigation for active TB disease among those with evidence of symptoms as well as the benefits associated with IPT will be important for increasing IPT provision. Additionally, South Africa recently released guidelines that remove the recommendation to place a TST prior to starting a patient on IPT.[15] This may result in greater provision of IPT and IPT provision should be re-evaluated under these new guidelines.

Conclusion

ART uptake has increased substantially among individuals with high CD4 counts in the UTT era in South Africa while IPT provision remains infrequent. While the findings presented in this dissertation are important for understanding HIV care in the UTT era in South Africa, the patient experience is likely far more complicated than what we were able to investigate based on the data we collected. The decision to test for HIV, initiate treatment, and remain engaged in care is often informed not only by a patient's personal interaction with a healthcare provider but also through their own understanding of HIV and ART and acceptance of their diagnosis, perceived and/or experienced HIV-related stigma, social support, and health systems issues including operating hours, waiting times, and confidentiality. Thus, future research focused on testing and treatment in the HIV care program should incorporate measures of psycho-social factors as well as clinic level factors that may influence treatment provision in order to gain a greater understanding of how these components factor into a patient's engagement in HIV care. Understanding these factors will aid in the design of patient-centric interventions that may encourage greater uptake of testing, ART, and improve long-term retention in care.

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12. National Department of Health Republic of South Africa. Fast tracking implementation of the 90-90-90 strategy for HIV, through implementation of the test and treat (TT) policy and same-day antiretroviral therapy (ART) initiation for HIV positive patients. Pretoria; 2017.

13. Lester R, Hamilton R, Charalambous S, Dwadwa T, Chandler C, Churchyard G, et al. Barriers to implementation of isoniazid preventive therapy in HIV clinics: A qualitative study. AIDS. 2010;24(Suppl. 5):S45–8.

14. Van Ginderdeuren E, Bassett J, Hanrahan C, Mutunga L, Van Rie A. Health system barriers to implementation of TB preventive strategies in South African primary care facilities. PLoS One. 2019;14(2):e0212035.

15. National Department of Health Republic of South Africa. 2019 ART clinical guidelines for the management of HIV in adults, pregnancy, adolescents, children, infants, and neonates. Pretoria; 2019.

Curriculum Vitae

KATE SHEARER

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EDUCATION

Johns Hopkins Bloomberg School of Public Health — Baltimore, Maryland
Doctor of Philosophy, Epidemiology — 2019 (Expected)

Emory University Rollins School of Public Health — Atlanta, Georgia
Master of Public Health, Global Epidemiology — 2010

Tulane University — New Orleans, Louisiana
Bachelor of Arts, Political Science — 2006

PUBLIC HEALTH AND RESEARCH EXPERIENCE

Health Economics and Epidemiology Research Office — Johannesburg, South Africa
Researcher, Epidemiology — Jul 2011 – Jul 2014

Centre for Infectious Disease Research in Zambia — Lusaka, Zambia
Fellow, *Prevention of Mother to Child Transmission* — Aug 2010 – Jun 2011

Virginia Department of Health — Richmond, Virginia
Volunteer Epidemiologist, Tuberculosis Control — May – Jul 2010

Centers for Disease Control and Prevention — Atlanta, Georgia
Research Assistant, Division of Tuberculosis Elimination — Jan – Apr 2010
Aug 2008 – Apr 2009

Emory University Rollins School of Public Health — Atlanta, Georgia
Graduate Research Assistant, Department of Epidemiology — Sep 2009 – Apr 2010

The Salvation Army World Service Office — Chikankata, Zambia
Intern, Chikankata Child Survival Project — May – Jul 2009

The Leukemia and Lymphoma Society — Atlanta, Georgia
School & Youth Intern — Jan – May 2008

TEACHING EXPERIENCE

Johns Hopkins University — Baltimore, Maryland
Teaching Assistant

Methodologic Challenges in Epidemiologic Research — Mar – May 2016
Epidemiologic Basis for Tuberculosis Control — Jan – Mar 2016
Jun 2016 (Summer Institute)
Jan – Mar 2017
Jun 2017 (Summer Institute)
Assessing Epidemiologic Impact of Human Rights Violations — Mar – May 2015

Section Leader
Fundamentals of Epidemiology Aug – Dec 2015

Emory University Rollins School of Public Health Atlanta, Georgia
Teaching Assistant
Epidemiologic Methods 1 Aug – Dec 2009

BOOK CHAPTERS

Stringer E, **Shearer K**. Breastfeeding among HIV-1 infected women: maternal health outcomes and social repercussions. In: Kourtis AP, Bulterys M, eds. *Human Immunodeficiency Virus type 1 (HIV-1) and Breastfeeding*. Advances in Experimental Medicine and Biology, 743, Springer US; 2012: 39-49.

JOURNAL PUBLICATIONS

Berhanu R, David A, da Silva P, **Shearer K**, Sanne I, Stevens W, Scott L. Peformance of Xpert MTB/RIF, Xpert Ultra, and Abbott Real Ti*m*e MTB for the detection of tuberculosis in a high HIV burden setting in Johannesburg: a pragmatic trial. *Journal of Clinical Microbiology.* 2018; 56(12): e00560-18.

Shearer K, Evans D, Xhosa B, Hirasen K, Bracken C, Mahomed K, Long L, Fox MP. Low prevalence of depressive symptoms among stable patients on antiretroviral therapy in Johannesburg, South Africa. *PLoS One.* 2018; 13(9): e0203797.

Hirasen K, Evans D, Maskew M, Sanne I, **Shearer K**, Govathson C, Malete G, Kluberg S, Fox MP. The right combination – treatment outcomes among HIV positive patients initiating first-line fixed-dose antiretroviral therapy in a public sector HIV clinic in Johannesburg, South Africa. *Clinical Epidemiology.* 2017; 10: 17-29.

Risher K, Kapoor S, Daramola AM, Paz-Bailey G, Skarbinksi J, Doyle K, **Shearer K**, Dowdy D, Rosenberg E, Sullivan P, Shah M. Challenges in the evaluation of interventions to improve engagement along the HIV care continuum in the United States: a systematic review. *AIDS and Behavior.* 2017; 21(7): 2101-2123.

Shearer K, Evans D, Moyo F, Rohr JK, Berhanu R, Van den Berg L, Long L, Sanne I, Fox MP. Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa. *Tropical Medicine and International Health.* 2017; 22(2): 221-231.

Shearer K, Clouse K, MacLeod W, Maskew M, Long L, Sanne I, Fox MP. Citizenship status and engagement in HIV care: An observational cohort study to assess the association between reporting a national ID number and retention in public-sector HIV care in Johannesburg, South Africa. *BMJ Open.* 2017; 7: e013908.

Rayne S, Lince-Deroche N, Hendrickson C, **Shearer K**, Moyo F, Michelow P, Rubin G, Benn C, Firnhaber C. Open access comprehensive breast care in a resource-limited environment in South Africa: a model that is more than cancer care. *BMC Health Services Research.* 2017; 17(1): 63.

Rohr JK, Ive P, Horsburgh CR, Berhanu RH, **Shearer K**, Maskew M, Long L, Sanne I, Basset J, Ebrahim O, Fox MP. Developing a predictive risk model for first-line antiretroviral therapy failure in South Africa. *Journal of the International AIDS Society*, 2016; 19: 20987.

Rohr JK, Ive P, Horsburgh CR, Berhanu RH, **Shearer K**, Maskew M, Long L, Sanne I, Fox MP. Marginal structural models to assess delays in second-line HIV treatment initiation in South Africa. *PLoS One.* 2016; 11(8): e0161469.

Schnippel K, **Shearer K**, Evans D, Berhanu R, Dlamini S, Ndjeka N. Predictors of mortality and treatment success during treatment for rifampicin resistant tuberculosis within the South African National TB Programme 2009 to 2011: a cohort analysis of the national case register. *International Journal of Infectious Diseases.* 2015; 39: 89-94.

Fox MP, **Shearer K**, Maskew M, Meyer-Rath G, Clouse K, Sanne I. Attrition through multiple stages of pre-treatment and ART HIV care in South Africa. *PLoS One*. 2014; 9(10): e110252.

Shearer K, Brennan A, Maskew M, Long L, Berhanu R, Sanne I, Fox MP. The relation between efavirenz vs. nevirapine and virologic failure in Johannesburg, South Africa. *Journal of the International AIDS Society,* 2014; 17: 19065.

Shearer K, Maskew M, Ajayi T, Berhanu R, Majuba P, Sanne I, Fox MP. Incidence and predictors of herpes zoster among ART-naïve patients initiating HIV treatment in Johannesburg, South Africa. *International Journal of Infectious Diseases,* 2014; 23(C): 56-62.

Brennan A, **Shearer K**, Maskew M, Long L, Sanne I, Fox MP. Impact of choice of NRTI in first-line antiretroviral therapy: A cohort analysis of stavudine vs. tenofovir. *Tropical Medicine and International Health,* 2014: 19(5): 490-498.

Brennan A, Maskew M, Ive P, **Shearer K**, Long L, Sanne I, Fox MP. Increases in regimen durability associated with the introduction of tenofovir at a large public-sector clinic in Johannesburg, South Africa. *Journal of the International AIDS Society.* 2013; 16: 18794.

Shearer K, Fox MP, Maskew M, Berhanu R, Long L, Sanne I. The impact of choice of NNRTI on short-term treatment outcomes among patients prescribed tenofovir and lamivudine in Johannesburg, South Africa. *PLoS One.* 2013; 8(8): e71719.

Clouse K, Pettifor A, **Shearer K**, Maskew M, Bassett J, Larson B, Van Rie A, Sanne I, Fox MP. Loss to follow-up before and after delivery among women testing HIV-positive during pregnancy in Johannesburg, South Africa. *Tropical Medicine and International Health.* 2013; 18(4): 451-460.

Schnippel K, Rosen S, **Shearer K**, Martinson N, Long L, Sanne I, Variava E. Costs of inpatient treatment for multi-drug resistant tuberculosis in South Africa. *Tropical Medicine and International Health*. 2013; 18(1): 109-116.

Fox MP, **Shearer K**, Maskew M, MacLeod W, Majuba P, MacPhail P, Sanne I. Treatment outcomes after 7 years of public-sector HIV treatment. *AIDS*. 2012; 26(14): 1823-1828.

Shearer K, Khosropour C, Stephenson R, Sullivan PS. Do bisexual men tell their female partners about having male partners? Results from a national online HIV prevention survey in the United States. *International Journal of Sexual Health*. 2012; 24(3): 195-204.

ORAL PRESENTATIONS

Berhanu R, Scott L, David A, da Silva P, Govender L, **Shearer K***, Stevens W. Advances in molecular diagnostics for pulmonary tuberculosis: Xpert MTB/RIF, Xpert Ultra, and RealTi*m*e MTB. Symposium: "New Innovations in the Fight to End TB." 48th Union World Conference on Lung Health, Guadalajara, Mexico, Oct 11-14, 2017. *Presenter

Ncayiyana J, Goel V, Escamilla V, **Shearer K**, Emch M, van Rie A, Stevens W, Scott L. Spatial-temporal analysis of mycobacterial load among primary health care facilities in Eastern Cape province, South Africa. 48th Union World Conference on Lung Health, Guadalajara, Mexico, Oct 11-14, 2017.

Shearer K, Dowdy D, Scott L, Berrie L, MacLeod W, Fox MP, Golub J, Stevens W. Has the threshold of case detection with Xpert MTB/RIF been reached in South Africa? 3rd international conference of the African Society for Laboratory Medicine, Cape Town, South Africa, Dec 3-8, 2016. *Oral poster

Evans D, Budgell E, **Shearer K**, Berhanu R, Long L, Rosen S. Predictors of mortality in patients diagnosed with preXDR and XDR TB – Results from the South African National TB Programme, 2009 to 2010. 46th Union World Conference on Lung Health, Cape Town, South Africa, Dec 2-6, 2015.

Evans D, Schnippel K, Budgell E*, **Shearer K**, Berhanu R, Rosen S, Long L, Ndjeka N. Treatment outcomes of DR-TB patients in South Africa, disaggregated by HIV status, as reported in a national electronic drug resistant TB register. 8th International AIDS Conference on HIV Pathogenesis, Treatment and Prevention, Vancouver, Canada, Jul 19-22, 2015. *Presenter

Fox MP, **Shearer K***, Maskew M, Sanne I. Current CD4 count, more than baseline, predictive of loss to follow up from HIV care. 6th South African AIDS Conference, Durban, South Africa, Jun 18-21, 2013. *Presenter

Fox MP, **Shearer K**, Maskew M. The need for quantitative bias analysis in HIV/AIDS research: the case of nevirapine vs. efavirenz on virologic failure in Johannesburg, South Africa. 17th International Workshop on HIV Observational Databases, Cavtat, Croatia, Apr 11-13, 2013.

Brennan A, **Shearer K**, Maskew M, Ive P, Sanne I, Fox MP. Antiretroviral treatment outcomes after the introduction of tenofovir in the public-sector in South Africa. 17th International Workshop on HIV Observational Databases, Cavtat, Croatia, Apr 11-13, 2013.

Schnippel K, Rosen S, Ndibongo B, **Shearer K**, Variava E, Martinson N, Sanne I. The cost of inpatient treatment for multi-drug resistant tuberculosis in South Africa. 7th AIDS and Economics Pre-Conference, Washington D.C., USA, oral presentation, Jul 20-21, 2012.

Shearer K*, Maskew M, Fox MP. A comparison of traditional and competing risks approaches to assess programmatic outcomes in an observational HIV treatment cohort in Johannesburg, South Africa. 45th Annual Society for Epidemiologic Research meeting, Minneapolis, USA, Jun 27-30, 2012. *Presented by Daniel Westreich, PhD

POSTER PRESENTATIONS

Shearer K, Golub J, Long L, Fox MP. The impact of a universal test and treat policy on CD4 at ART initiation at an urban, public sector HIV treatment facility in Johannesburg, South Africa. 9th IAS Conference on HIV Science, Paris, France, Jul 23-26, 2017.

German D, **Shearer K**, Flynn C, Latkin C, Laeyendecker O, Quinn T, Clarke W. Examination of unrecognized and misreported HIV status in Baltimore MSM and PWID. 24th Conference on Retroviruses and Opportunistic Infections, Seattle, USA, Feb 13-16, 2017.

Shearer K, Variava E, Qomfo C, Cohn S, Chon S, Motlhaoleng K, Moulton L, Martinson N, Golub J. Prescribing ART for HIV-infected individuals with CD4 counts >350 cells/mm^3. Will clinicians actually test and treat newly diagnosed patients with higher CD4 counts? Evidence from South Africa. 20th International Workshop on HIV Observational Databases, Budapest, Hungary, Apr 7-9, 2016.

German D, **Shearer K**, Park JN, Flynn C, Latkin C, Laeyendecker O, Quinn T, Clarke W. Misreported HIV status and recalculated prevalence of unrecognized HIV infection in Baltimore MSM. 23rd Conference on Retroviruses and Opportunistic Infections, Boston, USA, Feb 22-25, 2016.

Govathson C, **Shearer K**, Evans D, Chasela C. The effect of tuberculosis infection on the body composition of HIV positive adult patients on ART in Johannesburg, South Africa. 7th SA AIDS Conference, Durban, South Africa, Jun 9-12, 2015.

Hendrickson C, Lince-Deroche N, Firnhaber C, Moyo F, **Shearer K**, Benn C, Rubin G, Michelow P, Rayne S. Characterization of breast disease presenting in HIV-positive and –negative patients at a public, tertiary hospital in Johannesburg, South Africa. 7th SA AIDS Conference, Durban, South Africa, Jun 9-12, 2015.

Hirasen K, Maskew M, Evans D, **Shearer K**, Govathson C, Malete G, Long L, Sanne I, Fox MP. Early treatment outcomes of patients initiated on fixed-dose combination therapy in a public sector HIV clinic in Johannesburg, South Africa. 7th SA AIDS Conference, Durban, South Africa, Jun 9-12, 2015.

Shearer K, Evans D, Xhosa B, Hirasen K, Bracken C, Mahomed K, Long L, Fox MP. Low prevalence of depressive symptoms amongst patients on antiretroviral therapy in Johannesburg, South Africa. 7th SA AIDS Conference, Durban, South Africa, Jun 9-12, 2015.

Rohr J, Ive P, Horsburgh CR, Berhanu R, **Shearer K**, Maskew M, Long L, Sanne I, Fox MP. Delaying second line therapy after first line failure: moderating effect of CD4 count. 22nd Conference on Retroviruses and Opportunistic Infections, Seattle, USA, Feb 23-26, 2015.

Rohr J, Ive P, Horsburgh CR, Berhanu R, **Shearer K**, Maskew M, Long L, Sanne I, Fox MP. Development of a predictive risk model for first line treatment failure. 22nd Conference on Retroviruses and Opportunistic Infections, Seattle, USA, Feb 23-26, 2015.

Schnippel K, **Shearer K**, Kamkuemah M, Berhanu R, Naicker M, Ndjeka N. Characteristics of patients treated for drug resistant tuberculosis as reported in the South

African Electronic Drug Resistant Tuberculosis Register (EDRWeb). 45th Union World Conference on Lung Health, Barcelona, Spain, Oct 28-Nov 1, 2014.

Lince-Deroche N, **Shearer K**, Firnhaber C, Hendrickson C, Moyo F, Teagle A, Benn C, Rubin G, Michelow P, Rayne S. The epidemiology of breast conditions at a public, tertiary hospital in Johannesburg, South Africa. 18th SIS World Congress on Breast Healthcare, Orlando, USA, Oct 16-19, 2014.

Rohr J, Ive P, Berhanu R, **Shearer K**, Maskew M, Long L, Sanne I, Fox MP. Effect of delays in switching to second line treatment in Johannesburg, South Africa. 20th International AIDS Conference, Melbourne, Australia, Jul 20-25, 2014.

Shearer K, Maskew M, Long L, Sanne I, Fox MP. Impacts of disaggregating programmatic outcomes by documentation of citizenship in South Africa. 20th International AIDS Conference, Melbourne, Australia, Jul 20-25, 2014.

Fox MP, **Shearer K**, Maskew M, Long L, Sanne I. Eight years experience with attrition and mortality on ART in South Africa. 18th International Workshop on HIV Observational Databases, Sitges, Spain, Mar 27-29, 2014.

Fox MP, **Shearer K**, Teagle A, Evans D, Long L, Sanne I. Long-term outcomes of over one thousand patients on second-line antiretroviral therapy in South Africa. 18th International Workshop on HIV Observational Databases, Sitges, Spain, Mar 27-29, 2014.

Shearer K, Clouse K, Evans D, Lince-Deroche N, Firnhaber C, Maskew M, Berhanu R, Long L, Fox MP. Cotrimoxazole use and immune system recovery among HIV-infected patients in South Africa. 18th International Workshop on HIV Observational Databases, Sitges, Spain, Mar 27-29, 2014.

Shearer K, Fox MP. Predictors and impact of suboptimal immune response in HIV-infected patients in South Africa. 18th International Workshop on HIV Observational Databases, Sitges, Spain, Mar 27-29, 2014.

Rohr J, Ive P, Berhanu R, **Shearer K**, Maskew M, Long L, Sanne I, Fox MP. Predictors of time to switch to second line ART after first line failure in Johannesburg, South Africa. 21st Conference on Retroviruses and Opportunistic Infections, Boston, USA, Mar 3-6, 2014.

Shearer K, Brennan AT, Maskew M, Berhanu R, Long L, Fox MP. Long-term virologic response in a cohort of HIV-infected patients in South Africa. 21st Conference on Retroviruses and Opportunistic Infections, Boston, USA, Mar 3-6, 2014.

Shearer K, Brennan A, Maskew M, Sanne I, Fox MP. The relation between NNRTI and virologic failure among HIV-infected patients in Johannesburg, South Africa. 6th South African AIDS Conference, Durban, South Africa, Jun 18-21, 2013.

Fox MP, **Shearer K**. Attrition through multiple stages of HIV care in South Africa: a challenge for test-and-treat. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, USA, Mar 3-6, 2013.

Shearer K, Maskew M, Majuba P, Sanne I, Fox MP. Incidence of herpes zoster among HIV-infected patients on antiretroviral therapy in Johannesburg, South Africa – who should we vaccinate? 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, USA, Mar 3-6, 2013.

Schnippel K, Rosen S, **Shearer K**, Martinson N, Sanne I, Variava E. The cost outcomes of inpatient treatment for multi-drug resistant tuberculosis in South Africa. 43rd Union World Conference on Lung Health, Kuala Lumpur, Malaysia, Nov 13-17, 2012.

Clouse K, **Shearer K**, Bassett J, Maskew M, Fox MP. Reduced loss to ART initiation among patients initiating cotrimoxazole prophylaxis therapy in Johannesburg, South Africa. 19th International AIDS Conference, Washington D.C., USA, Jul 22-27, 2012.

Fox MP, **Shearer K**, Maskew M, Brennan A, Sanne I. Incident pulmonary tuberculosis on antiretroviral therapy: 7 years of experience at the Themba Lethu Clinic in Johannesburg, South Africa. 19th International AIDS Conference, Washington D.C., USA, Jul 22-27, 2012.

Shearer K, Joseph J, Chibwesha C, Stringer E. Prior knowledge of HIV-infection at first ANC visit and its impact on ART initiation compared to women newly diagnosed at first visit in Lusaka, Zambia. 19th International AIDS Conference, Washington D.C., USA, Jul 22-27, 2012.

Fox MP, **Shearer K**. Differences in virologic suppression and treatment failure over the first year on ART among patients on tenofovir comparing those given efavirenz to those given nevirapine. 16th International Workshop on HIV Observational Databases, Athens, Greece, Mar 29-31, 2012.

Fox MP, **Shearer K**, Maskew M, Brennan A, Long L, Majuba P, Sanne I. Short term impacts of a change in ART initiation threshold for patients co-infected with TB in Johannesburg, South Africa. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, USA, Mar 5-8, 2012.

Fox MP, **Shearer K**, Maskew M, MacLeod W, Majuba P, MacPhail P, Sanne I. HIV treatment outcomes after seven years in a large public-sector HIV treatment program in Johannesburg, South Africa. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, USA, Mar 5-8, 2012.

Schuttner L, Zijdel W, Manda H, **Shearer K**, Siyingwa R, Theis M, Mwaba L, Zue C, Musatwe D, Roos D, Mwansa N, Mwalukanga M, Nyakubaya L, Stringer JSA, Chi BH, Chintu N. Use of mobile phone-guided community outreach for integrated primary health care and HIV services in Zambia. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, Jul 17-20, 2011.

HONORS AND AWARDS

Johns Hopkins Bloomberg School of Public Health	
R Bradley Sack Family Award	2017 – 2018
Charlotte Silverman Award	2016 – 2017
HIV Epidemiology and Prevention Sciences T32 Pre-Doctoral Trainee	2014 – 2016
Global Health Established Field Placement Award	2015
UJMT NIH Fogarty Global Health Scholar (pre-doctoral)	2016 – 2017
Emory University Global Field Experience Award	2009
Tulane University Academic Merit Scholarship	2004 – 2006

PROFESSIONAL AFFILIATIONS

Member, International Union against Tuberculosis and Lung Disease	2017 – Present

Member, Society for Epidemiologic Research	2012 – Present
Member, International AIDS Society	2012 – Present