Assessing Tuberculosis Preventive Therapy (TPT) Outcomes in PLHIV: Initiation, Completion Rates and Influencing Factors within the DROP TB Cohort study in KwaZulu-Natal province, South Africa

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Abstract

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Introduction: Tuberculosis (TB) is a major global health concern, particularly among people living with HIV (PLHIV). The incidence of TB/HIV co-infection is particularly high in Sub-Saharan Africa, specifically in the KwaZulu-Natal province of South Africa. The World Health Organization (WHO) recommends tuberculosis preventative therapy (TPT) to prevent TB disease in PLHIV. Despite the proven benefits of TPT in reducing TB incidence and mortality among PLHIV, its implementation faces numerous challenges in high-burden areas like KwaZulu-Natal. The uptake and completion of TPT is hindered by several factors, such as logistical, structural, socio-economic, socio-demographic, behavioral, clinical, and healthcare resource challenges. This thesis study aims to assess the TPT initiation and completion rate and explore their associated factors among enrolled PLHIV newly starting or reinitiating antiretroviral therapy (ART) within the Diagnostic Routines for HIV-infected Outpatients with TB (DROP TB) cohort study, providing insights of TPT outcomes in a high TB burden setting and offering valuable implications for public health interventions and policymaking.

Methods: This secondary data analysis utilized the prospective DROP TB cohort study. The participants were clinic-based PLHIV, aged 18 years and above, enrolled at two public health clinics, one peri-urban and one rural, situated in the uMkhanyakude district. The study assessed TPT initiation and completion rates among PLHIV participants who were screened for TB at the time of ART initiation or re-initiation between November 2021 and April 2024. TPT regimens provided during the study period were 6H (six months daily isoniazid, (H)) and in September 2023, 3HP (3 months weekly isoniazid (H) and rifapentine (P)) was introduced. Enrolled participants were assessed for various factors during baseline and quarterly check-in phone calls or in-person visits at months 3, 6, 9, and 12, coordinated with the participant's ART refill visits when possible. TPT initiation and completion rates were assessed using selected variables from the DROP TB dataset, including socio-demographic, behavioral, and clinical data, as well as TPT-related reasons. Quarterly follow-up interviews and medical record reviews were used to assess TPT initiation and completion. South African national guidelines recommended that clinics provide TPT to PLHIV after TB disease was excluded with TB screening. TPT completion was determined through case-by-case outcome assessments based on the completion of follow-up visits according to the medication duration of TPT regimen (6-month follow-up for 6H or 3-month follow-up for 3HP). Both univariate and multivariate analyses by modified Poisson regression were employed to identify factors associated with TPT initiation and completion.

Results: Among 411 enrolled PLHIV participants, 96% (393/411) were eligible for TPT, and 75% (293/393) initiated TPT, with the majority 79% (232/293) initially receiving 6H and 21% (61/293) receiving the 3HP regimen. However, during follow-up visits, 34 6H participants restarted or changed to 3HP, resulting in a final TPT regimen distribution of 27% (80/293) on 3HP and 73% (213/293) on 6H regimen. Of the 293 PLHIV who initiated TPT, 18% (52/293) were excluded from the TPT completion analysis due to unknown TPT completion status. Among participants with known TPT completion status, less than half 42% (102/241) completed their prescribed TPT regimen. TPT initiation rates were higher among participants enrolled at the rural clinic *(82% vs. 71%, aRR: 1.21, 95% CI: 1.08-1.36, p=0.001)* and those who were unemployed compared to employed *(65% vs. 35%, aRR: 0.87, 95% CI: 0.77-1.00, p=0.034)*. Notably, while 86% (25/29) of

participants who were prescribed 3HP completed the regimen, only 36% (77/212) of those prescribed 6H completed the full 6-month course. TPT completion was 21% higher among males *(aRR: 1.21, 95% CI: 0.78-1.88)*, 52% higher among unemployed participants *(aRR: 1.52, 95% CI: 0.97-2.38)*, 32% lower among those having secondary and above education *(aRR: 0.68, 95% CI: 0.43-1.09)*, 64% lower among those aged >50 years *(aRR: 0.36, 95% CI: 0.12-1.10)*, compared to their respective reference groups, although these associations did not reach statistical significance. The risk of TPT non-completion was 59% lower for 3HP compared to 6H regimen in univariate analysis *(RR: 0.41, 95% CI: 0.29-0.60, p<0.001)* and remained significant in the multivariate analysis adjusted for age, sex, employment, education, enrollment site, and housing type *(aRR: 0.42, 95% CI: 0.29-0.60, p<0.001)*. The strong association between 3HP and higher completion rates persisted in sensitivity analyses assuming either non-completion or completion for regimen changed participants with unknown completion status.

Conclusion: Nearly three-quarters of PLHIV in this cohort started TPT along with ART, with higher rates among rural clinic enrollees and unemployed individuals, but less than half completed their regimen. The only significant predictor of TPT completion was regimen, with participants receiving 3HP more likely to complete than those receiving 6H, emphasizing the need for shorter, more patient-friendly regimens. While not statistically significant, the study found that TPT completion rates were higher among males, unemployed participants, and those aged <30 years, while completion rates were lower among those aged >50 years and with higher education levels. Given the absence of strong determinants of TPT completion beyond regimen type in our analysis, further research is needed to investigate the potential influence of healthcare system-related issues, individual patient preferences, and other factors on TPT completion rates, as the current study did not find statistically significant associations between most socio-demographic, behavioral factors and treatment completion. The study emphasizes the need to promote shorter regimens like 3HP, provide targeted counseling and support to patients at risk of non-completion, and equip healthcare facilities with resources and training to increase TPT uptake and completion rates among PLHIV in high-burden settings.

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Figures and Tables

1. Introduction

Tuberculosis (TB) continues to be a major global health concern, with a particularly severe deadly impact among people living with HIV (PLHIV). The World Health Organization (WHO) reported approximately 10 million new TB cases in 2022, with a significant proportion of these occurring in PLHIV[1]. TB is a disease that is typically curable and preventable, however, ranked as the second leading cause of death worldwide from a single infectious agent in 2022 after coronavirus disease (COVID-19)[1]. The death toll from TB was nearly double that of HIV/AIDS[1]. Additionally, the intersection of TB and HIV infections exacerbates the public health crisis. TB is responsible for one third of HIV-associated deaths globally[2]. In people without HIV or other risk factors, the lifetime likelihood of latent TB infection reactivation is 10%, with 5% developing TB disease within the first 2 to 5 years following infection[3,4]. This risk significantly escalates in cases of immunosuppression, particularly when associated with HIV infection[4]. The combination of HIV and TB can be deadly, and TB is the leading cause of death among PLHIV in resource-limited countries[5]. According to the WHO's estimation, in countries with a significant HIV epidemic, PLHIV face a 20 to 37 times greater chance of becoming ill with TB compared to those without HIV[4].

South Africa ranks among the top 10 countries with the highest TB burdens worldwide, reporting a TB incidence rate of 513 cases per 100,000 population in 2021[6]. Among those diagnosed with TB, 4.1% had multi-drug resistant (MDR-TB)/rifampicin-resistant TB (RR-TB) and 0.4% had pre-extensively drug-resistant TB (XDR-TB), while TB remains the leading cause of death in PLHIV [6]. KwaZulu-Natal province in South Africa is notable for its exceptionally high TB and HIV rates, with an estimated HIV-TB co-infection rate of around 70% among people diagnosed with TB[7]. The province is also reported to have one of the highest HIV prevalence rates worldwide, which has a substantial impact on the TB epidemic [8]. KwaZulu-Natal and Gauteng Provinces have the highest HIV prevalence in South Africa, 17.6% and 11.8%, respectively, accounting for nearly half of the country's total HIV burden, while the

Western Cape and Northern Cape have the lowest prevalence. According to a provincial analysis, Gauteng (21%), KwaZulu-Natal (19%), Eastern Cape (16%), Mpumalanga, and Limpopo account for nearly 80% of all new HIV infections in South Africa in 2021[6]. Moreover, based on the 2021 Global Burden of Disease (GBD) Disability-Adjusted Life Years (DALYs) data, KwaZulu-Natal's TB prevalence was 2.5 times higher than the global trend (1553.9 vs 595.3 DALYs per 100,000) and slightly lower than the South African regional trend of 1811.3 DALYs per 100,000[9]. Similarly, KwaZulu-Natal's HIV prevalence was remarkably high, with a rate of 10152.3 DALYs per 100,000, which is nearly 19 times higher than the global trend of 510.3 DALYs per 100,000[9] (Figure 1).

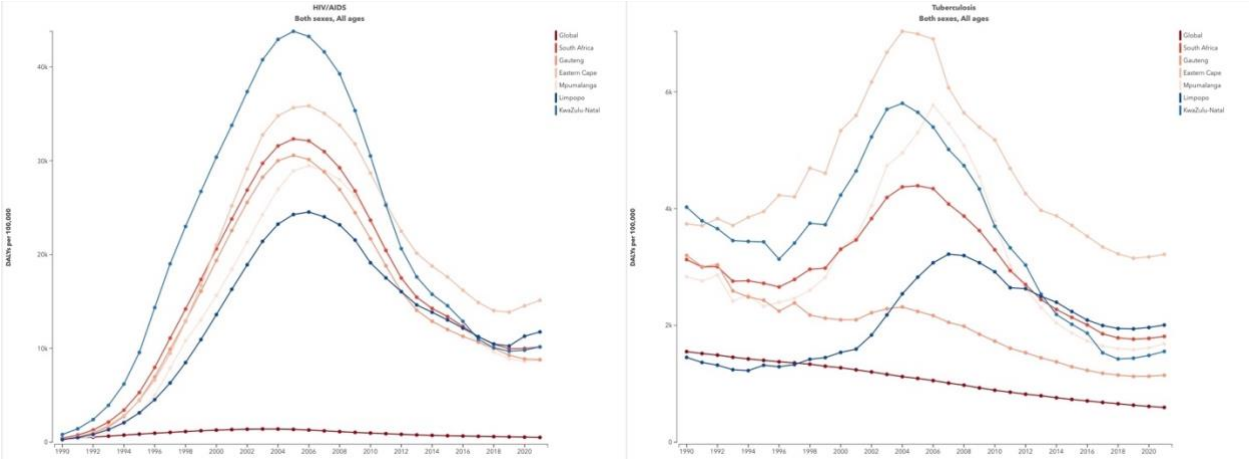

Figure 1: Provincial trends in HIV/AIDS and tuberculosis prevalence in Disability-Adjusted Life Years (DALYs) of South Africa from 1990 to 2021 (Image from GBD Dashboard https://vizhub.healthdata.org/gbd-compare/)

To mitigate the impact of TB among PLHIV, the WHO recommends TB preventive therapy (TPT)[3]. A crucial part of the WHO End TB Agenda is the prevention of active TB disease through TPT [3,10]. TPT involves a course of one or more anti-tuberculosis drugs to prevent TB and only those infected or exposed to TB bacteria and at higher risk of acquiring TB are given TPT[3]. The WHO recommends providing TPT to all PLHIV who are unlikely to have active TB, as part of comprehensive HIV care, regardless of their level of immunosuppression or the availability of latent TB infection (LTBI) testing[3]. Numerous studies have demonstrated the significant advantages of isoniazid preventive therapy (IPT) for PLHIV in terms of reduced mortality rates among PLHIV. Isoniazid monotherapy for 6 to 12 months demonstrates

effectiveness between 60% and 90%[11]. Furthermore, the TEMPRANO clinical trial found that IPT contributed to a 37% reduction in all-cause mortality among PLHIV, regardless of baseline CD4 cell count or ART initiation timing[12]. In high TB-impacted areas with limited resources, PLHIV who consistently adhere to IPT experience a notable 20% decrease in mortality risk[13]. The other WHO recommended TPT regimens such as the 3-month once-weekly rifapentine and isoniazid (3HP) regimen is equally effective as isoniazid monotherapy, but has higher completion rates and lower risk of hepatotoxicity [3,14,15]. The WHO recommends providing IPT for 6 months or longer durations depending on the population and settings, based on the TB/HIV burden[3]. Previous studies have shown that the efficacy of 6 months of IPT is not significantly different from that of 12 months of IPT[3]. According to South African ART clinical guidelines, all PLHIV starting or already on ART who have not yet received TPT should be considered for TPT after ruling out active TB, unless they have contraindications[16,17]. Both the 2020 and updated 2023 guidelines recommend different TPT regimens based on age and pregnancy status, with the additional recommendation of the 3HP regimen in the 2023 guidelines: non-pregnant PLHIV adults over 15 years are recommended isoniazid (INH) daily for 12 months or rifapentine and isoniazid once-weekly for 3 months (3HP) based on availability; PLHIV children under 15 years are recommended INH daily for 6 months, and pregnant PLHIV women are recommended INH daily for 12 months[17]. Pyridoxine is recommended to be given with all regimens containing INH. In practice, many clinics provide 6 months of INH for non-pregnant PLHIV.

During the UN High-Level Meeting on Tuberculosis in 2018, there was a significant emphasis on enhancing TPT delivery, aiming to treat 30 million people by 2022[1]. However, during the five years from 2018 to 2022, only 15.5 million individuals received TPT, achieving just 52% of the intended 30 million target[1]. As TB remains a leading cause of mortality among PLHIV, improving TPT outcomes is crucial for global TB control efforts, especially in regions with high TB/HIV co-infection rates. Despite the proven benefits, the implementation of TPT remains fraught with challenges. A study by Baloyi et al. demonstrated that healthcare workers' skepticism about TPT's efficacy, under prioritization in practice, disagreement over

implementation responsibility, resource limitations, poor reporting standards, limited patient education on TPT, and socio-economic barriers affecting patient access all contribute to low TPT uptake and completion rates in South Africa[18].

While the national South African national guidelines include provisions for TPT as part of HIV care[17], its TPT uptake varies significantly across regions[6]. In KwaZulu-Natal, where the disease burden is severe, TPT implementation is particularly challenging due to logistical and systemic issues like drug shortages and insufficient staffing in healthcare facilities[18]. These challenges result in lower completion rates for TPT in the region, compounded by socio-economic conditions and geographical barriers that limit access to healthcare[18]. A study of Baloyi et al. also indicated that only 53% of eligible PLHIV initiated TPT in KwaZulu-Natal, with a lower completion rate (61%) than Western Cape and Eastern Cape, and a majority lost to follow-up, indicating serious TPT implementation issues[18]. Additionally, socio-economic factors such as unemployment, low income, and concerns over crime have indirectly affected the accessibility of health services and influenced TPT outcomes[18].

The determinants that influence TPT uptake and completion are diverse and multifaceted, involving socio-demographic, socioeconomic, behavioral, clinical, and healthcare resource issues. Research in Malawi indicates that socio-demographic aspects, particularly younger individuals and males, are less likely to complete TPT than females[19]. Furthermore, studies have demonstrated a positive relationship between female gender and TPT adherence, with women being more likely to complete the medication[5,19]. According to a recent study, TPT uptake in PLHIV is significantly higher among those in the highest wealth group living in urban areas than among those in the lowest income group[20]. Behavioral factors like smoking and alcohol use also have an impact on TPT adherence. Although specific data on these issues is limited, general patterns of increased alcohol use and smoking are related with lower medication adherence among PLHIV, which may have an adverse effect on TPT adherence. For instance, the study in Uganda discovered a link between increased alcohol intake and poor TPT adherence [21], while a Cape Town study reported that PLHIV who smoke or consume

alcohol are four times less likely to complete TPT[22]. Clinical factors such as CD4 cell count, ART adherence, and viral load are important in managing both tuberculosis and HIV, and they are linked to TPT adherence[21]. Furthermore, PLHIV at WHO stage 3 or 4 with CD4 levels between 100-349 cells/mm^3 have been linked to reduced TPT completion rates compared to CD4 >350 cells/mm^3 [23]. Healthcare resource-related barriers, such as inconsistent pharmaceutical supply, infrastructurel limitations, and different levels of healthcare provider engagement, are detrimental to TPT adherence and completion, particularly in resource-limited settings[24]. These findings highlight the importance of including a variety of socio-demographic, socioeconomic, behavioral, clinical and systemic aspects into interventions intended at increasing TPT uptake and completion among PLHIV.

Despite extensive research demonstrating the effectiveness of TPT for PLHIV, there is a notable lack of comprehensive data regarding TPT initiation and completion rates, as well as the associated factors influencing these rates, particularly in high-burden areas such as KwaZulu-Natal, South Africa. Understanding the entire TPT cascade, from initiation to completion, and the factors that influence these stages in the KwaZulu-Natal region is crucial for developing targeted and effective public health interventions aimed at improving health outcomes for PLHIV. Additionally, current reporting requirements from funders for TPT implementation primarily focus on TPT initiation metrics. This focus can potentially lead to an overestimation of the true coverage and expected impact of TPT if there are high rates of non-completion among those who initiate treatment, resulting in poor completion rates and sub-optimal programme implementation[25]. To address this research gap in understanding TPT cascade of uptake and completion in programmatic settings, this study aims to analyze both TPT initiation and completion rates, thereby contributing essential data to inform and improve national programs and policies.

2. Methods

2.1. Study Design

The Diagnostic Routines for HIV-infected Outpatients with TB (DROP TB) study is a prospective, observational diagnostic validation study evaluating the performance of the FLOW-TB (Salus Discovery) test, a novel rapid urine-based assay detecting mycobacterial lipoarabinomannan (LAM), for diagnosing TB in PLHIV outpatients initiating or re-initiating ART in rural KwaZulu-Natal, South Africa[26]. The diagnostic accuracy of the FLOW-TB test will be assessed by comparing its performance to TB sputum culture and Xpert MTB/RIF Ultra. This thesis study is nested cohort study by performing secondary data analysis of the prospective DROP TB study dataset, utilizing selected variables from socio-demographic data (age, sex, marital status, education level, employment, housing type), behavioral data (smoking and alcohol consumption), clinical data (CD4 count, BMI, ART regimen, prior TB history, TPT regimen) and enrollment sites, as well as data on TPT-related reasons. Data from medical charts were utilized to analyze both TPT initiation and completion rates. Additionally, patient surveys and medical chart data were combined to collect information on the reasons for TPT status, including reasons for not giving or stopping TPT at each follow-up visit.

2.2. Study setting

KwaZulu-Natal, a province located in the eastern region of South Africa, has a population of 11.29 million and accounting for 20.8% of the country's total population as of 2022[27]. It is the second most populous province in South Africa after Gauteng. Administratively, KwaZulu-Natal is divided into one metropolitan municipality (eThekwini metropolitan municipality) and 10 district municipalities (Figure 2), which are further subdivided into 43 local municipalities[27].

Umkhanyakude district municipality, situated in the northernmost part of KwaZulu-Natal, is one of the ten districts in the province. It has a population of 689,090, representing 5.9% of KwaZulu-Natal's total population[28]. The district faces significant challenges such as high unemployment

and poverty, with most of its residents living below the poverty line[28]. Umkhanyakude has the highest Multi-Poverty Index (MPI) among the top 10 districts in South Africa, indicating a high level of poverty[28]. The district's population is relatively young, with 50.7% of its residents being under the age of 18. More than 70% of the unemployed population is younger than 35 years old[28]. Furthermore, the district has high levels of adult illiteracy, with more than 27% of adult females and 22% of adult males having not received any form of schooling[28].

Regarding its health profile, Umkhanyakude District Municipality has the highest malaria prevalence and HIV prevalence in the province. Between 20-30% of adults are HIV-positive, and the district has the second-highest HIV prevalence rate at 41.1%, which is higher than both the provincial and national averages. Tuberculosis is also a major cause of mortality in the district[28].

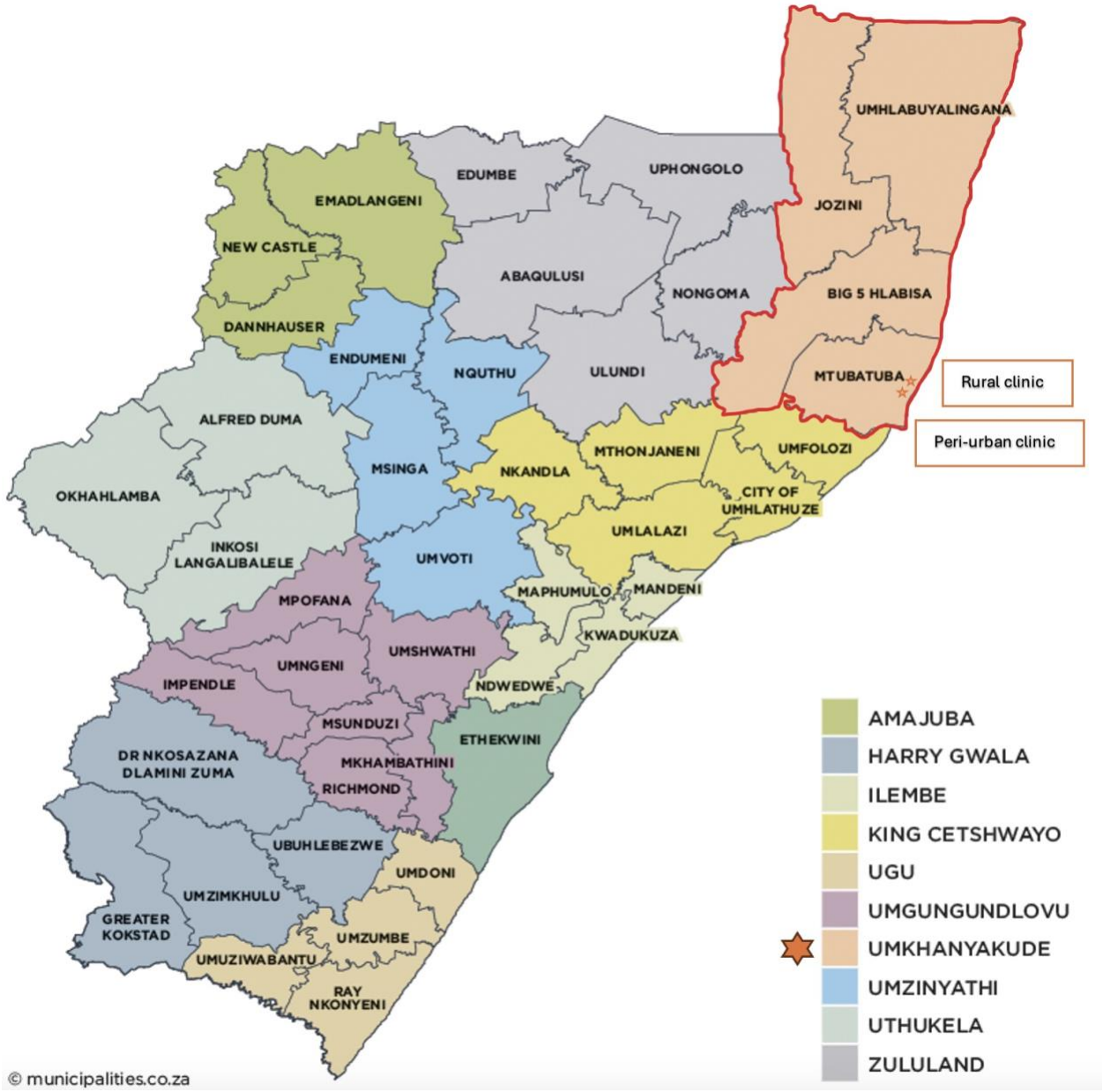

Figure 2: Map of Peri-urban and Rural study clinic study sites in uMkhanyakude district municipality, KwaZulu-Natal province, South Africa (Reference: https://municipalities.co.za/provinces/view/4/kwazulu-natal)

2.3. Procedures

The study enrolled clinic-based PLHIV adults, aged 18 years and above, at two public health clinics for 24 months, with an additional 12 months for follow-up completion[26]. Participants were enrolled from two Department of Health (DoH) clinics, one peri-urban and one rural, situated in

the uMkhanyakude district (Figure 2). For this study, the TPT initiation and completion rates were assessed among PLHIV participants who were screened for TB at the time of ART initiation or re-initiation at two public clinics between November 2021 and April 2024. The Study Research Nurse (SRN) identified eligible participants, obtained informed consent, and administered baseline questionnaires collecting socio-demographic, behavioral, and clinical data. According to South African national guidelines, all PLHIV initiating or re-initiating ART should be tested for TB with a symptom screening and sputum nucleic acid test (Xpert Ultra). The DROP-TB study augmented this baseline screening with a sputum TB culture test as well. Participants diagnosed with TB at baseline screening were registered and initiated on TB treatment. The DROP TB study's data collection utilizes REDCap, a secure and password-protected electronic database approved by the US National Institute of Health (NIH) for clinical research[26]. A core questionnaire, which includes variables such as demographic data, TB exposure history, clinical history, health behaviors, and medication, was administered to all participants. Additional data, including results from laboratory tests like CD4 counts and TB tests, were collected by participant ID number and integrated into the database[26]. At the conclusion of the baseline visit, participants moved from the research clinic to a clinical consultation room for initiation of ART and other therapies as indicated. All treatment decisions were made by DOH nurses and recorded in patient clinical charts based on national guidelines.

2.4. Follow-up

Participants were observed for 12 months to assess TB diagnosis, treatment, ART initiation, TPT initiation, hospitalizations, and vital status. Assessing clinical status was done at a Week 1 phone call, followed by quarterly check-in phone calls or in-person visits at months 3, 6, 9, and 12, coordinated with the participant's ART refill visits when possible[26]. Additionally, clinic chart reviews, laboratory database reviews, and searches of the district TB register were conducted quarterly to identify interim diagnoses. The study coordinator checked lab results daily, and positive TB Xpert MTB/RIF and urine Alere LF-LAM results were reviewed with the study support clinician to coordinate registration and enrollment for TB treatment[26]. Negative TB test results

were conveyed during the next follow-up visit, and for positive TB test results, the study nurse confirmed the participant's arrival at the clinic and linkage to care with the TB nurse[26]. At each follow-up visit, the study team conducted a TB symptom screen and recorded any ART initiation, TPT initiation, TB diagnosis, and treatment, as well as the reasons for non-initiation of these treatments. For TPT, eligible participants were started on the appropriate regimen, after their TB screening results were assessed. There were two TPT regimens, 6 months daily oral isoniazid (6H) regimen and 3 months of once-weekly rifapentine and isoniazid (3HP) regimen in this study. 6H was the only TPT available until September 2023 when 3HP was introduced in public clinics as a second option to non-pregnant adults. Quarterly follow-up interviews and medical record reviews were used to assess TPT initiation and completion.

2.5. TPT completion definitions for non-regimen changed participants

A specific manual outcome assessment approach was used to establish the primary outcome variable for TPT completion. First, the tentative TPT completion date was determined based on the TPT regimen from the initiation date, which was 6 months for 6H and 3 months for 3HP regimen. Using the data cutoff date of end of April 2024, the outcome assessment for each participant was conducted by examining the recorded reasons for not giving or stopping TPT according to the medical chart and patient survey from each follow-up visit. TPT completion was identified if a participant completed a 6-month follow-up for 6H or a 3-month follow-up for 3HP regimen. Within this dataset, a participant was considered to have completed TPT if they were recorded as "Yes, continued TPT" at 2 consecutive follow-up visits (3 month, 6 month) for 6H and 1 completed follow-up (3 month) for the 3HP regimen. Additionally, one participant on 6H regimen was counted as a TPT completer due to being recorded as completed in the medical chart at month 9 follow-up visit.

Summary table for TPT completion definition for non-regimen changed particpants

TPT regimen	Duration	TPT completion – "Yes" definition for analysis
Isoniazid Preventive Therapy (IPT) – 6H • PLHIV adult >15 years: 6 months daily, oral, isoniazid 300mg (INH) with daily pyridoxine 25 mg	6 months	- Recorded as "Yes, continued TPT" after initiation with up to 2 consecutive follow-up visits (6 months) ***One 6H participant recorded as completed in the medical chart at month 9 follow-up visit*
3 months of once-weekly rifapentine (RPT) and isoniazid (INH) - 3HP • Non-pregnant PLHIV: up to 3 tablets of FDC 300mg INH and 300mg RPT, weekly for 12 weeks based on body weight and age	3 months (Once-weekly for 12 weeks)	- Recorded as "Yes, continued TPT" after initiation with 1 completed follow-up visit (3 months)

2.6. TPT completion definitions for regimen changed participants and unknown TPT completion status

Among participants who initiated TPT, participants with unknown completion status were due to either administratively censored outcomes resulting from insufficient follow-up by the data cutoff date of April 2024 or missing follow-up data after switching from the 6H to the 3HP regimen. Of these, some participants were administratively right-censored due to insufficient follow-up time. Additionally, some participants initially on the 6H regimen switched to the 3HP regimen after initiation. These participants were classified as TPT completers, TPT non-completers, or having an unknown TPT completion status based on the timing and duration of the regimen change and the availability of follow-up data. Specifically, Participants who switched from 6H to 3HP after initiation (with less than 3 months on 6H) and completed at least one follow-up visit after restarting 3HP continuously without any interruption in follow-up, within the data cutoff date,

were counted as having a final 3HP regimen. Participants who switched from 6H to 3HP (with at least 3 months on 6H) but had an interrupted follow-up visit before restarting 3HP were assumed to have interrupted 6H and restarted 3HP, and were counted as having a final 6H regimen. Participants with administratively right-censored outcomes and those with missing follow-up data were excluded from the TPT completion analysis. However, sensitivity analyses were employed by imputing the unknown TPT completion status of those regimen-changed participants with missing follow-up data. The manual imputation was done by creating completion status either "Yes" or "No" for those participants with missing follow-up data after switching regimens. The remaining participants who did not complete TPT were assessed based on the recorded reasons for not giving or discontinuing TPT, as documented in the medical charts or patient surveys from each follow-up visit.

Summary table for definitions of TPT completers, non-completers and final regimen for regimen changed participants

Participant groups	Final regimen for regimen changed	Definitions
TPT completer	3HP	- Participants who switched from 6H to 3HP after initiation (with less than 3 months on 6H) and completed at least one follow-up visit after restarting 3HP continuously without any interruption in follow-up, within the data cutoff date.

		These participants were counted as having a final 3HP regimen.
TPT non-completer	6H	- Participants who switched from 6H to 3HP (with at least 3 months on 6H) but had an interrupted follow-up visit before restarting 3HP. These participants were assumed to have interrupted 6H and restarted 3HP, and were counted as having a final 6H regimen.

2.7. Statistical analysis

The initial data management of the DROP TB cohort dataset was performed using R studio version 4.3.3 (2024-02-29) and Microsoft Excel version 16.83, and the final data analysis was conducted in R studio version 4.3.3 (2024-02-29). Categorical variables were reported as percentages, while continuous variables such as age, CD4, and BMI were presented with median and interquartile range (IQR) for both TPT initiation and completion status. Body Mass Index (BMI) was categorized based on the Centers for Disease Control and Prevention (CDC) adult BMI categories: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), and overweight (>25 kg/m²)[29]. CD4 counts were

categorized according to the CDC CD4 categories definition: category 1 (≥500 cells/mm^3), category 2 (200–499 cells/mm^3), and category 3 (<200 cells/mm^3) [30].

TPT initiation was explored among all eligible screened PLHIV participants of DROP TB cohort, while TPT completion analysis included only participants with completed follow-up status according to the TPT completion definition, excluding those with unknown completion status of right-censored and missing follow-up (Figure 3.). The reasons for both non-initiation and non-completion were summarized (Figure 3.) according to the reasons recorded from medical charts of "reasons treatment not started" and patient surveys of "if not started TPT, why not?", "not eligible for TPT", and "eligible but not started TPT" from each follow-up visit. In this cohort, The TPT initiation regression analysis accounted for participants with the initial regimen before switching regimens, and TPT completion regression analysis was accounted for participants with the final regimen after changing from 6H to 3HP based on the definition of TPT completion for regimen-changed participants.

In addition to the literature review, a directed acyclic graph (DAG) was created using the web-based DAGitty version 3 to explore potential confounders[31]. Univariable and multivariable analyses were conducted using robust (modified) Poisson regression to assess the independent effects of socio-demographic, behavioral, clinical and systemic factors on the binary outcome of TPT initiation and completion. Poisson regression was chosen over logistic regression to analyze the binary outcome data, as odds ratios from logistic regression may overestimate risk when the outcome event is common. Poisson regression with robust error variances was employed to directly estimate Risk Ratios (RRs), which are more intuitive to interpret in a public health context and provide stable estimates despite sparse data or small sample size[32]. Poisson regression with robust variance estimates was employed to calculate both unadjusted (RR) and adjusted risk ratios (aRR) with 95% confidence intervals (CI). Variance inflation factor (VIF) was checked to assess multicollinearity, and all models showed VIF scores of less than 5, indicating no significant collinearity among the covariates (Supplemental table 7). Statistical significance was set at a p-value ≤0.05. Besides the exploration of potential confounders with DAG and literature review,

covariate analysis using stepwise regression in both directions was performed, and covariates were selected based on Akaike information criterion (AIC) score comparison. Based on univariate analysis, stepwise regression, and predefined confounders from DAG and literature review, three models were constructed with constant covariates. After checking the goodness of fit for the three models, the final model was selected based on AIC score and adjusted R^2 (model performance metric) by comparing it with the full model. The model 1 was selected as final model based on lowest AIC and highest adjusted R^2 among all three models (Supplemental table 7). The final multivariable model included the exposures of employment, CD4, BMI, smoking status, alcohol use, and TPT regimens, while adjusting for the potential confounders of age, sex, employment, education, enrollment site, and housing.

2.8. Consent and Ethical approval

The ethical framework of this thesis study adheres to the stringent requirements set by institutional review boards and ethics committees. Ethical approval for the primary DROP TB study was obtained from the University of Washington IRB (STUDY00006518), with additional approvals from the UKZN Biomedical Research Ethics Committee and the London School of Hygiene and Tropical Medicine Ethics Committee obtained prior to the commencement of the study[26]. Participants were thoroughly briefed on the study through the informed consent process in either English or isiZulu, ensuring their understanding and voluntary participation. Consent is documented in writing and participants maintain the right to withdraw from the study at any stage[26].

3. Results

3.1. Participant characteristics

Among the 411 PLHIV participants enrolled, 393 (96%) were eligible for TPT initiation, while 18 (4%) were not eligible after initial TB symptom screening and diagnosis (Figure 3). During TB

screening, 13 PLHIV were newly diagnosed with TB, 4 PLHIV were found ineligible for TPT, and 1 PLHIV died. TPT non-eligible PLHIV participants were excluded from this study of TPT outcome assessment (Figure 3). The majority of the 393 TPT-eligible PLHIV participants were female (61%), aged 30-50 years old (57%) with a median age of 32 years (IQR: 26, 39), enrolled at the peri-urban clinic (65%), not married but in a relationship or partnership (80%), had secondary education or above (85%), were unemployed (66%), and lived in formal housing or apartments (79%) (Table 1). The majority of participants were non-smokers (76%), while 51% reported alcohol consumption at baseline assessment. Most PLHIV participants reported a new HIV diagnosis at the time of the enrollment visit (89%), had a CD4 count of 200-500 cells/mm^3 (44%) with a median CD4 count of 350 cells/mm^3 (IQR: 191, 519), and had normal body weight (55%) with a median BMI of 23.3 kg/m^2 (IQR: 20.5, 27.6) at baseline. The fixed-dose combination (FDC) of ART consisting of tenofovir, lamivudine, and dolutegravir (TDF/3TC/DTG) was the major ART regimen prescribed (95%) among PLHIV participants (Table 1).

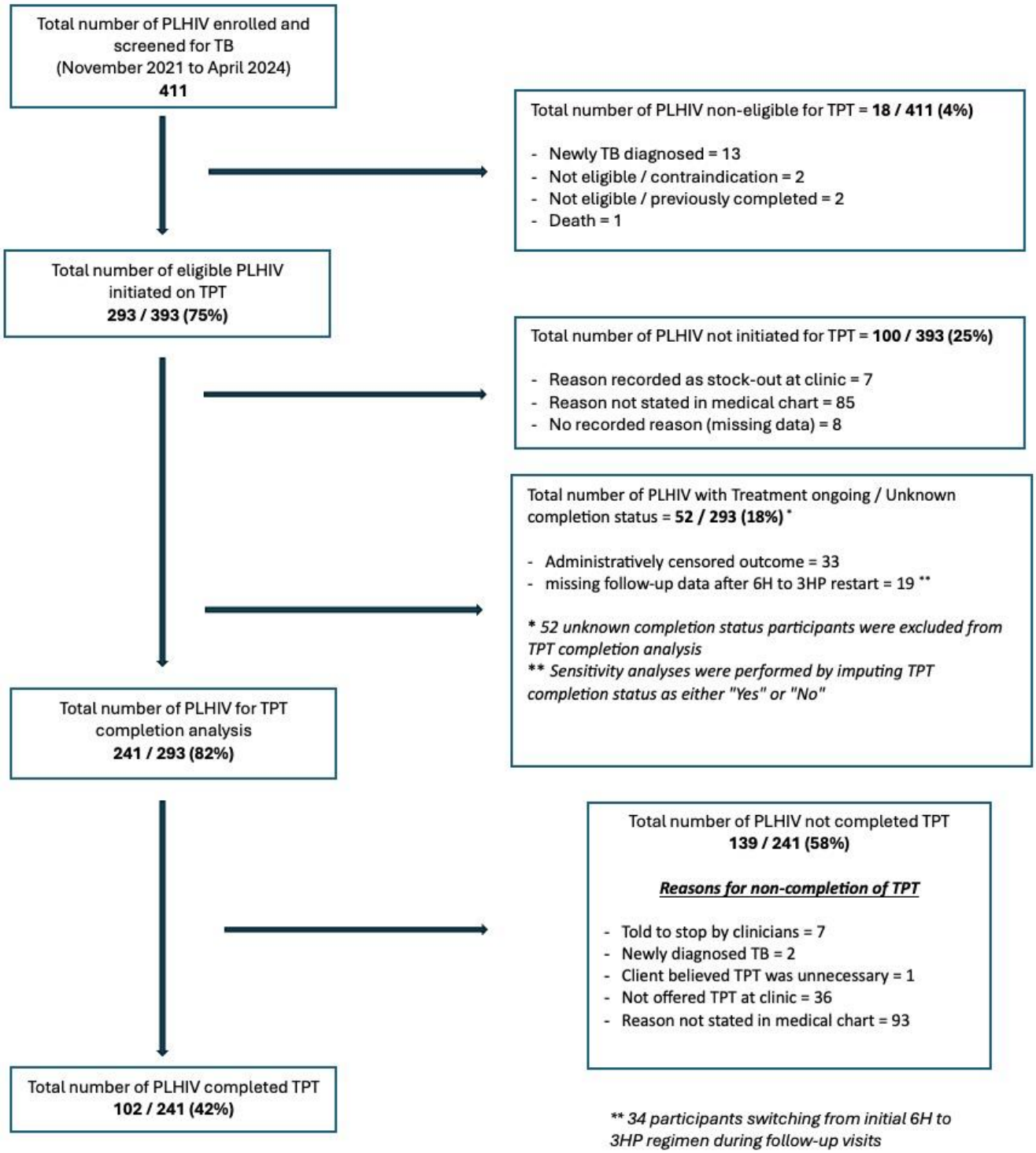

Figure 3: Flow diagram of TPT initiation and completion among enrolled PLHIV participants within DROP TB cohort study from November 2021 to April 2024

3.2. TPT initiation

Of the 393 TPT-eligible PLHIV participants, 293 (75%) initiated TPT, with the majority initially initiated on 6H regimen 232 (79%) and 61 (21%) on the 3HP regimen (Table 1). Among the 232 participants initially initiated on 6H, 34 had their regimen changed or restarted with 3HP during follow-up visits. Of these, 19 were recorded 3HP as their final regimen, while 15 were recorded 6H as their final regimen based on the definition of TPT completion for regimen changed participants. As a result, the final TPT regimens were 6H for 73% (213/293) of participants and 3HP for 27% (80/293) of participants (Table 1). Among 293 TPT-initiated participants, the higher proportion were aged 30-50 years (57%) with a median age of 32 years (IQR: 26, 38), not married but in a partner or relationship (79%), unemployed (65%), had secondary education or above (85%), and lived in formal housing or apartments (79%) (Table 1). Most TPT-initiated PLHIVs (74%) had a CD4 count of <200 cells/mm^3 with a median CD4 count of 359 cells/mm^3 (IQR: 197, 538), and 56% had a normal body weight with a median BMI of 22.9 kg/m^2 (IQR: 20.5, 27.5) (Table 1). About one-quarter (25%) of participants reported smoking and half of them (52%) reported alcohol use (Table 1). The initiation is higher among participants who enrolled at the rural clinic, with 82% (111/136) compared to the peri-urban clinic, which has 71% (182/257) (Table 3). After reviewing the reasons for non-initiation of TPT for 100 participants, as recorded in patient surveys and medical charts, it was found that 7 PLHIV participants did not initiate TPT due to a medication stock-out at the clinic. For the majority of participants who did not initiate TPT, no reason was documented in their medical charts (Figure 3).

Table 1: Socio-demographic, behavioral, and clinical factors for TPT initiation among DROP TB study participants

			TPT initiation status	
Variables	**Category**	**Overall (N = 393)**	**No (N = 100)**	**Yes (N = 293)**
Age	*Median (IQR)*	32 (26, 39)	34 (26, 39)	32 (26, 38)
Age category	*<30 years*	37% (147/393)	36% (36/100)	38% (111/293)
	30-50 years	57% (224/393)	58% (58/100)	57% (166/293)
	>50 years	6% (22/393)	6% (6/100)	5% (16/293)
Sex	*Female*	61% (240/393)	61% (61/100)	61% (179/293)
	Male	39% (153/393)	39% (39/100)	39% (114/293)
BMI	*Median (IQR)*	23.3 (20.5, 27.6)	23.5 (21.0, 27.8)	22.9 (20.5, 27.5)
BMI category	*Normal weight (18.5–24.9 kg/m²)*	55% (215/393)	51% (51/100)	56% (164/293)
	Overweight (>25 kg/m²)	37% (145/393)	39% (39/100)	36% (106/293)
	Underweight (<18.5 kg/m²)	8% (33/393)	10% (10/100)	8% (23/293)
Enrollment sites	*Peri-urban clinic*	65% (257/393)	75% (75/100)	62% (182/293)
	Rural clinic	35% (136/393)	25% (25/100)	38% (111/293)
Marital status	*Married*	5% (21/393)	5% (5/100)	5% (16/293)
	Not married (partnered/relationship)	80% (313/393)	83% (83/100)	79% (230/293)
	Single	15% (59/393)	12% (12/100)	16% (47/293)
Employment	*Employed*	34% (133/393)	30% (30/100)	35% (103/293)
	Unemployed	66% (260/393)	70% (70/100)	65% (190/293)
Housing Type	*Formal housing / Apartment*	79% (311/393)	79% (79/100)	79% (232/293)
	Informal housing	1% (4/393)	1% (1/100)	1% (3/293)
	Traditional / RDP housing	19% (75/393)	20% (20/100)	19% (55/293)
	Missing	0.8% (3/393)	0	3
Education level	*Primary*	12% (47/393)	13% (13/100)	12% (34/293)
	Secondary and above	85% (333/393)	83% (83/100)	85% (250/293)
	Unknown	3% (13/393)	4% (4/100)	3% (9/293)
Smoking status	*Yes*	24% (96/393)	24% (24/100)	25% (72/293)
	No	76% (297/393)	76% (76/100)	75% (221/293)
Alcohol consumption	*Yes*	51% (201/393)	50% (50/100)	52% (151/293)
	No	49% (192/393)	50% (50/100)	48% (142/293)
HIV status	*Newly HIV positive*	89% (348/393)	86% (86/100)	89% (262/293)
	Prior HIV positive	11% (45/393)	14% (14/100)	11% (31/293)
Prior TB history	*Prior TB treated - No*	88% (345/393)	85% (85/100)	89% (260/293)
	Prior TB treated - Yes	12% (48/393)	15% (15/100)	11% (33/293)
CD4 count	*Median (IQR)*	348 (191, 519)	345 (179, 470)	359 (197, 538)
	Missing	11	6	5
CD4 category	*<200 cell/mm³*	26% (101/393)	27% (27/100)	74% (74/293)
	200-500 cell/mm³	44% (171/393)	47% (47/100)	42% (124/293)
	>500 cell/mm³	28% (110/393)	20% (20/100)	31% (90/293)
	Missing	3% (11/393)	6	5
ART regimen[1]	*TEE (TDF/FTC/EFV)*	0.8% (3/393)	0	1% (3/293)
	TLD (TDF/3TC/DTG)	95% (372/393)	87% (87/100)	97% (285/293)
	Missing	5% (18/393)	13	5
Initial TPT regimen[2]	*3HP*	16% (61/393)	0	21% (61/293)
	IPT (6H)	59% (232/393)	0	79% (232/293)
	No TPT	25% (100/393)	100% (100/100)	0
Final TPT regimen[2]	*3HP*	20% (80/393)	0	27% (80/293)
	IPT (6H)	54% (213/393)	0	73% (213/293)
	No TPT	25% (100/393)	100% (100/100)	0

[1] *ART = Antiretroviral Therapy, TDF/3TC/DTG = tenofovir, lamivudine, dolutegravir, TDF/FTC/EFV = tenofovir, emtricitabine, efavirenz*

[2] *TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive Treatment (6 months daily isoniazid), 6H = 6 months of daily isoniazid*

3.3. TPT completion

Among 293 TPT-initiated participants, TPT completion status was unknown for 52 (18%) participants: 33 participants had administratively censored outcomes due to insufficient follow-up by the data cutoff date of April 2024, and 19 participants had missing follow-up status after restarting the 3HP regimen from 6H. It is important to note that 34 (12%) participants on 6H switched to the 3HP regimen after initiation. Out of the 34 participants who switched regimens, 14 participants had an interrupted follow-up visit between 3HP restart, and those participants were assumed to have interrupted 6H and restarted 3HP based on TPT completion definition of regimen changed participants. In the analysis, these participants were counted as having a final 6H regimen and considered as TPT non-completers. Two 6H participants who changed to 3HP completed one follow-up visit after restarting. These participants were counted as having a final 3HP regimen and considered as TPT completers. The remaining participants who switched to 3HP but had missing follow-up data after restarting treatment were counted as having an unknown TPT completion status, with the assumption that they were still ongoing treatment. Thus, there were a total of 52 participants with unknown TPT completion status.

After excluding 52 participants with unknown TPT completion status, 241 (82%) participants were analyzed for TPT completion status. Among the 241 TPT-initiated participants who had enough time for follow-up with known completion status, 102 (42%) completed their prescribed TPT regimens. Out of the 102 participants who completed TPT, 75% (76 participants) were recorded as having up to 2 continuous follow-up visits for 6H and 25% (25 participants) were recorded 1 follow-up visit completed for 3HP after initiation dates. One participant on the 6H regimen was considered a TPT completer based on their medical chart record at month 9 follow-up visit. Among 102 TPT completers, a high proportion were female (63%), 53% were aged 30-50 years with a median age of 32 years (IQR: 24, 37), 61% were enrolled at a peri-urban clinic, 77% were not married but had a partner or relationship, 84% had secondary or above education, 74% were unemployed, and 78% lived in formal housing or apartments (Table 2). Participants who completed TPT had CD4 counts distributed relatively evenly across <200 cells/mm^3 (25%), 200-

500 cells/mm³ (42%), and >500 cells/mm³ (32%) categories, with a median CD4 count of 361 cells/mm³ (IQR: 202, 545). For BMI, participants (56%) were of normal weight with a median BMI of 22.9 kg/m² (IQR: 20.5, 27.2). Among TPT-completed PLHIV participants, 73% were recorded as non-smokers, and 51% were recorded as never having used alcohol (Table 2). Participants who had 3HP as their final TPT regimen achieved an 86% (25/29) completion rate, whereas those on the 6H regimen had a 36% (77/212) completion rate (Table 4).

According to reasons recorded in the patient survey and medical chart review for 139 TPT non-completed participants, 7 participants were told to stop by clinicians during follow-up visits, but it was not specifically stated whether this was due to side effects or other contraindications of the TPT regimen. Two participants were newly diagnosed with TB, and one participant stopped TPT because they believed it was unnecessary. For 36 participants, the reason for not completing TPT was recorded as not being offered TPT at the clinic, without specifying if this occurred before initiation or during follow-up. For the majority of TPT non-completed participants (67%), the reason was not stated in their medical charts (Figure 3).

Table 2: Socio-demographic, behavioral, and clinical factors for TPT completion among TPT-initiated DROP TB study participants

		TPT completion status		
Variables	**Category**	**Overall (N = 241)**	**No (N = 139)**	**Yes (N = 102)**
Age	*Median (IQR)*	32 (26, 38)	33 (27, 38)	32 (24, 37)
Age category	*<30 years*	37% (91/241)	33% (46/139)	44% (45/102)
	30-50 years	56% (136/241)	69% (82/139)	53% (54/102)
	>50 years	5.8% (14/241)	8% (11/139)	3% (3/102)
Sex	*Female*	62.2% (150/241)	63% (86/139)	63% (64/102)
	Male	38.0% (91/241)	38% (53/139)	37% (38/102)
BMI calculation	*Median (IQR)*	23.3 (20.5, 27.5)	23.4 (20.7, 27.7)	22.9 (20.5, 27.2)
BMI category	*Normal weight (18.5–24.9 kg/m²)*	55.0% (132/241)	54% (75/139)	56% (57/102)
	Overweight (>25 kg/m²)	37.3% (90/241)	39% (54/139)	35% (36/102)
	Underweight (<18.5 kg/m²)	8.0% (19/241)	10% (10/139)	9% (9/102)
Enrollment sites	*Peri-urban clinic*	61.0% (147/241)	61% (85/139)	61% (62/102)
	Rural clinic	39.0% (94/241)	39% (54/139)	39% (40/102)
Marital status	*Married*	5.8% (14/241)	7% (9/139)	5% (5/102)
	Not married (partnered/relationship)	77.2% (186/241)	78% (108/139)	77% (78/102)
	Single	17.0% (41/241)	16% (22/139)	19% (19/102)
Employment	*Employed*	35.7% (86/241)	42% (59/139)	27% (27/102)
	Unemployed	64.3% (155/241)	58% (80/139)	74% (75/102)
Housing Type	*Formal housing / Apartment*	80.1% (193/241)	82% (114/139)	78% (79/102)
	Informal housing	0.8% (2/241)	0.7% (1/139)	1% (1/102)
	Traditional / RDP housing	18.0% (43/241)	16% (22/139)	21% (21/102)
	Missing	1.2% (3/241)	2	1
Education level	*Primary*	12.4% (30/241)	12% (17/139)	13% (13/102)
	Secondary and above	84.0% (202/241)	84% (116/139)	84% (86/102)
	Unknown	4.0% (9/241)	4% (6/139)	3% (3/102)
Smoking status	*Yes*	25.0% (60/241)	23% (32/139)	28% (28/102)
	No	75.1% (181/241)	77% (107/139)	73% (74/102)
Alcohol consumption	*Yes*	51.0% (123/241)	53% (73/139)	49% (50/102)
	No	49.0% (118/241)	48% (66/139)	51% (52/102)
HIV status	*Newly HIV positive*	88.4% (213/241)	89% (123/239)	88% (90/102)
	Prior HIV positive	11.2% (28/241)	12% (16/139)	12% (12/102)
Prior TB history	*Prior TB treated - No*	88.4% (216/241)	89% (124/139)	90% (92/102)
	Prior TB treated - Yes	11.6% (25/241)	11% (15/139)	10% (10/102)
CD4 count	*Median (IQR)*	367 (201, 543)	368 (201, 542)	361 (202, 545)
	Missing	3	2	1
CD4 category	*<200 cell/mm³*	24.5% (59/241)	25% (34/139)	25% (25/102)
	200-500 cell/mm³	41.4% (100/241)	41% (57/139)	42% (43/102)
	>500 cell/mm³	33.0% (79/241)	33% (46/139)	32% (33/102)
	Missing	1.2% (3/241)	2	1
ART regimen[1]	*TEE (TDF/FTC/EFV)*	1.2% (3/241)	1% (2/139)	1% (1/102)
	TLD (TDF/3TC/DTG)	97.0% (233/241)	95% (132/139)	99% (101/102)
	Missing	2.1% (5/241)	5	0
Final TPT regimen[2]	*3HP*	12.0% (29/241)	3% (4/139)	25% (25/102)
	IPT (6H)	88.0% (212/241)	97% (135/139)	78% (77/102)

[1] *ART = Antiretroviral Therapy, TDF/3TC/DTG = tenofovir, lamivudine, dolutegravir, TDF/FTC/EFV = tenofovir, emtricitabine, efavirenz*

[2] *TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive Treatment (6 months daily isoniazid), 6H = 6 months of daily isoniazid*

3.3. TPT initiation, completion and correlates (univariate analysis)

Univariate analyses were conducted to explore the factors associated with both TPT initiation and completion status among socio-demographic, behavioral, clinical factors and enrollment site. In the univariate analysis for TPT initiation, TPT initiation was significantly associated with employment status and clinic (Table 3). The risk of TPT initiation was 14% lower among unemployed participants compared to employed participants *(RR: 0.86, 95% CI: 0.76, 0.97, p = 0.016)*. Participants enrolled at the rural clinic had 21% higher TPT initiation compared to those enrolled at the peri-urban clinic *(RR: 1.21, 95% CI: 1.08, 1.36, p = 0.001)* (Table 3). No other sociodemographic, behavioral, or clinical factors, including TPT regimen, were associated with TPT initiation (Table 3).

In the univariate analysis for TPT completion, only the TPT regimen was a strong predictor of TPT completion, showing a statistically significant association, while sex, age, employment and education showed non-significant associations. Marital status, CD4, BMI, housing, enrollment sites, smoking, and alcohol consumption showed no association with TPT completion in the unadjusted analysis (table 4). The risk of TPT non-completion was 59% lower for the 3HP regimen compared to the 6H regimen *(RR: 0.41, 95% CI: 0.29-0.60, p<0.001)*. Older participants aged >50 years had a 65% higher risk of TPT non-completion compared to younger participants aged <30 years *(RR: 0.35, 95% CI: 0.11-1.07, p = 0.065)*, while unemployed participants had a 50% higher risk of TPT completion compared to employed participants *(RR: 1.50, 95% CI: 0.94-2.39, p = 0.086)*; both associations were borderline statistically significant. Male participants had a 22% higher risk of TPT completion, while being underweight had a 20% lower risk of TPT completion, and having secondary and above education had a 31% lower risk of TPT completion compared to their respective reference levels (Table 4).

Table 3: Factors influencing TPT initiation in DROP TB study: Univariate and Multivariate regression analyses adjusted for age, sex, employment, education, enrollment site, and housing

			Unadjusted			Adjusted		
Variables	**Category**	**N = 393 n/N[1]**	**RR[3]**	**95% CI[2]**	**p-value**	**aRR[4]**	**95% CI[2]**	**p-value**
Sex	*Female* ***(ref)***	179/240						
	Male	114/153	0.94	0.81, 1.10	0.448	0.94	0.81, 1.10	0.433
Age category	*< 30 years* ***(ref)***	111/147						
	30-50 years	166/224	0.92	0.80, 1.10	0.233	0.93	0.81, 1.06	0.285
	>50 years	16/22	0.92	0.67, 1.28	0.632	0.94	0.68, 1.30	0.721
CD4 category	*<200 cell/mm³* ***(ref)***	74/101						
	200-500 cell/mm³	124/171	0.98	0.83, 1.17	0.833	0.97	0.82, 1.16	0.756
	>500 cell/mm³	90/110	1.11	0.94, 1.31	0.209	1.10	0.93, 1.30	0.261
	Missing	11						
BMI category	*Normal weight* ***(ref)***	164/215						
	Overweight	106/145	0.92	0.81, 1.05	0.234	0.93	0.82, 1.06	0.290
	Underweight	23/33	0.99	0.80, 1.21	0.903	1.00	0.82, 1.23	0.952
Marital status	*Married* ***(ref)***	16/21						
	Not married (partnered/relationship)	230/313	0.98	0.75, 1.28	0.880			
	Single	47/59	1.14	0.85, 1.53	0.382			
Housing type	*Formal housing / Apartment* ***(ref)***	232/311						
	Informal housing	3/4	0.92	0.63, 1.35	0.679	0.98	0.68, 1.41	0.908
	Traditional / RDP housing	55/75	0.98	0.83, 1.16	0.839	0.98	0.83, 1.16	0.822
	Missing	3						
Education level	*Primary* ***(ref)***	34/47						
	Secondary and above	250/333	1.10	0.89, 1.35	0.377	1.07	0.88, 1.32	0.487
	Unknown	9/13	0.88	0.58, 1.34	0.552	0.91	0.60, 1.37	0.638
Employment	*Employed* ***(ref)***	103/133						
	Unemployed	190/260	0.86	0.76, 0.97	**0.016**	0.87	0.77, 1.00	**0.034**
Enrollment sites	*Peri-urban clinic* ***(ref)***	182/257						
	Rural clinic	111/136	1.21	1.08, 1.36	**0.001**	1.21	1.08, 1.36	**0.001**
Smoking status	*No* ***(ref)***	221/297						
	Yes	72/96	1.03	0.87, 1.22	0.736	1.03	0.87, 1.22	0.757
Alcohol consumption	*No* ***(ref)***	142/192						
	Yes	151/201	1.00	0.88, 1.12	0.937	1.00	0.88, 1.12	0.909
Initial TPT regimen[5]	*3HP* ***(ref)***	61/293						
	IPT (6H)	232/293	1.00	0.78, 1.30	>0.99	1.00	0.75, 1.36	>0.99

[1] *n (completed - Yes) / N (overall)*
[2] *95% Confidence interval*
[3] *Risk ratio,*
[4] *adjusted Risk ratio*
[5] *TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive Treatment, 6H = 6 months of daily isoniazid*

3.4. TPT initiation, completion and correlates (multivariate analysis)

Based on covariate analysis and model performance metrics, the final model selected was adjusted for sex, age, employment, education, enrollment site, and housing (Supplemental Table 7). In the multivariate adjusted analysis, TPT initiation showed a statistically significant association with employment and enrollment site, consistent with the unadjusted analysis. Unemployed participants had a 13% lower risk of TPT initiation compared to employed participants *(RR: 0.87, 95% CI: 0.77, 1.00, p = 0.034)*. Participants enrolled at the rural clinic had a 21% higher TPT initiation rate compared to those enrolled at the peri-urban clinic *(RR: 1.21, 95% CI: 1.08, 1.36, p = 0.001)*. In the multivariate adjusted analysis for TPT completion, TPT regimen still showed a significant association with completion; the 3HP regimen had a 58% lower risk of TPT non-completion compared to the 6H regimen *(aRR: 0.42, 95% CI: 0.29-0.60, p<0.001)* (Table 4). Older participants aged >50 years still showed a non-significant association of a 64% higher risk of TPT non-completion compared to younger participants aged <30 years *(aRR: 0.36, 95% CI: 0.12-1.10, p = 0.074)*, while unemployed participants had the same non-significant association of a 52% higher risk of TPT completion compared to employed participants *(aRR: 1.52, 95% CI: 0.97-2.38, p = 0.069)* (Table 4). The associations of being male with a 21% higher risk of completion, and having secondary and above education with a 32% lower risk of TPT completion compared to their respective reference levels were almost the same as in the unadjusted analysis (Table 4). Participants living in informal housing had a 21% higher risk of TPT completion compared to those living in formal housing or apartments in the adjusted analysis, which was a non-significant association (Table 4). Similar to the unadjusted analysis, marital status, CD4, BMI, enrollment sites, smoking, and alcohol consumption showed no association with TPT completion in the adjusted analysis (Table 4).

Table 4: Factors influencing TPT completion in DROP TB study: Univariate and Multivariate regression analyses adjusted for age, sex, employment, education, enrollment site, and housing

			Unadjusted			Adjusted		
Variables	**Category**	**N = 241 n/N[1]**	**RR[3]**	**95% CI[2]**	**p-value**	**aRR[4]**	**95% CI[2]**	**p-value**
Sex	*Female* ***(ref)***	64/150						
	Male	38/91	1.22	0.78, 1.90	0.387	1.21	0.78, 1.88	0.393
Age category	*< 30 years* ***(ref)***	45/91						
	30-50 years	54/136	0.84	0.60, 1.18	0.315	0.85	0.60, 1.19	0.342
	>50 years	3/14	0.35	0.11, 1.07	0.065	0.36	0.12, 1.10	0.074
CD4 category	*<200 cell/mm³* ***(ref)***	25/59						
	200-500 cell/mm³	43/100	1.04	0.72, 1.48	0.851	1.01	0.71, 1.43	0.951
	>500 cell/mm³	33/79	1.05	0.70, 1.57	0.807	1.03	0.70, 1.53	0.865
	Missing	3						
BMI category	*Normal weight* ***(ref)***	57/132						
	Overweight	36/90	1.00	0.75, 1.33	0.974	1.00	0.75, 1.35	0.986
	Underweight	9/19	0.80	0.51, 1.24	0.317	0.81	0.52, 1.26	0.349
Marital status	*Married* ***(ref)***	5/14						
	Not married (partnered/relationship)	78/186	0.89	0.47, 1.70	0.733			
	Single	19/41	1.06	0.51, 2.23	0.873			
Housing type	*Formal housing / Apartment* ***(ref)***	79/193						
	Informal housing	1/2	1.13	0.20, 6.31	0.885	1.21	0.25, 5.88	0.816
	Traditional / RDP housing	21/43	1.10	0.77, 1.55	0.602	1.09	0.78, 1.54	0.586
	Missing	3						
Education level	*Primary* ***(ref)***	13/30						
	Secondary and above	86/202	0.69	0.42, 1.15	0.157	0.68	0.43, 1.09	0.112
	Unknown	3/9	0.74	0.29, 1.90	0.533	0.76	0.30, 1.90	0.551
Employment	*Employed* ***(ref)***	27/86						
	Unemployed	75/155	1.50	0.94, 2.39	0.086	1.52	0.97, 2.38	0.069
Enrollment sites	*Peri-urban clinic* ***(ref)***	62/147						
	Rural clinic	40/94	0.92	0.66, 1.29	0.631	0.91	0.65, 1.28	0.604
Smoking status	*No* ***(ref)***	78/181						
	Yes	28/60	1.05	0.73, 1.51	0.766	1.10	0.74, 1.52	0.741
Alcohol consumption	*No* ***(ref)***	52/118						
	Yes	50/123	0.95	0.68, 1.33	0.766	0.94	0.68, 1.31	0.732
Final TPT regimen[5]	*3HP* ***(ref)***	25/29						
	IPT (6H)	77/212	0.41	0.29, 0.60	**<0.001**	0.42	0.29, 0.60	**<0.001**

[1]n (completed - Yes) / N (overall)
[2]95% Confidence interval
[3]Risk ratio,
[4] adjusted Risk ratio
[5]TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive , 6H = 6 months of daily isoniazid

3.5. Sensitivity analyses for regimen changed participants with missing follow-up data

In a set of sensitivity analyses, we imputed the completion status as "Yes" or "No" for the 19 participants with unknown outcomes who were missing follow-up data after changing regimen from 6H to 3HP (Figure 3). These sensitivity analyses were employed for both the unadjusted (Supplemental Table 5) and adjusted (Supplemental Table 6) models, using the same final model, adjusting for age, sex, employment, education, enrollment site, and housing type. The results were then compared to the final model without the imputed outcomes. It is important to note that in the sensitivity analysis with imputed completion status as "Yes", 92% (44/48) of 3HP initiators were 3HP completers, while with imputed status as "No", 52% (25/48) of 3HP initiators were 3HP completers, compared to 86% (25/29) who were 3HP completers in the final model (supplemental table 5 and 6). Based on the sensitivity analyses, the 6H regimen was associated with lower TPT completion rates compared to the 3HP regimen in the final unadjusted *(RR 0.41, 95% CI 0.29-0.60)* and adjusted models *(aRR 0.42, 95% CI 0.29-0.60)*. This association remained significant when imputing "Yes" for missing TPT completion status *(unadjusted RR 0.40, 95% CI 0.30-0.54; adjusted aRR 0.40, 95% CI 0.30-0.54)* but became non-significant upon imputing "No" *(unadjusted RR 0.71, 95% CI 0.41-1.23; adjusted aRR 0.71, 95% CI 0.41-1.24)*. The association between being male and higher TPT completion was attenuated in both "Yes" *(unadjusted RR 1.17, 95% CI 0.80-1.71; adjusted aRR 1.18, 95% CI 0.80-1.72)* and "No" *(unadjusted RR 1.05, 95% CI 0.64-1.72; adjusted aRR 1.10, 95% CI 0.65-1.77)* imputation scenarios compared to the final models. The non-significant association with being unemployed and higher risk of TPT completion compared to employed remained consistent across sensitivity analyses. Similarly, having secondary and above education showed a non-significant association with lower TPT completion risk compared to primary education in sensitivity analyses, aligning with the primary analysis. The association between age >50 years and lower TPT completion compared to age <30 years was also consistent. Other variables like CD4 category, BMI, housing type, enrollment sites, smoking, and alcohol consumption remained non-significant across all adjusted and unadjusted sensitivity analyses. These analyses indicate the primary IPT regimen finding's robustness when assuming completion for unknowns but attenuation when assuming non-completion.

4. Limitations

The primary aim of the DROP TB cohort study was to assess the diagnostic accuracy of FLOW-TB (Salus Discovery), a novel urine LAM test for tuberculosis detection. The questionnaires, methodology, and data collected were primarily focused on the DROP TB study's main objectives. Therefore, there are limitations regarding the availability of TPT-related data, such as the absence of pill count and adherence information, which could potentially introduce measurement or information bias in the estimation of TPT uptake and completion. Additionally, there was a lack of time-to-event data, including dates of TPT discontinuation, completion, or loss to follow-up. Consequently, the TPT completion outcome for this thesis analysis was primarily based on medical chart review data from the dataset. This reliance may lead to information bias or missing data bias due to potential missing entries by service providers or data entry errors related to patient outcomes. There might be a possible impact of COVID-19 on TPT uptake and completion, such as loss to follow-up, but it is challenging to assess this impact for the cohort due to limited data access. Additionally, there were unexpected regimen changes from the initial 6H to 3HP, which was not recommended by most guidelines including WHO and national guidelines, but the reasons for the regimen changes were not recorded. This lack of information on the rationale behind the regimen changes could introduce potential bias or confounding in the analysis of TPT completion, as the factors influencing the regimen changes are unknown. It's also important to note that there might be recall or social desirability bias for self-reported survey questionnaires regarding smoking and alcohol consumption. Lastly, this thesis study mainly focused on only two public clinics with PLHIV adults >18 years old in one district, which might cause limited generalizability to other settings or populations.

5. Discussion

This study evaluated TPT initiation and completion rates and explored their correlates among PLHIV over a 29-month period at two public clinics in KwaZulu-Natal Province, South Africa. The findings show that among eligible PLHIV, nearly three-quarters (75%) initiated TPT, but less than

half of those initiators (42%) completed their prescribed TPT regimen. These rates are suboptimal compared to the UN High-Level Meeting on TB's 90% coverage target for uptake and completion among contacts, PLHIV, and other eligible populations by 2027[1]. Similarly, the TPT completion rate from this study is very low compared to the WHO's global median completion rate of 87% among PLHIV who started TPT in 2020[1]. However, the TPT initiation rate in this study is slightly higher than recent studies in sub-Saharan Africa, which showed initiation rates of 41% in Tanzania[33], 42% in Kenya[34], 42% in South Africa[35], 45% in Namibia[36], 58% in KwaZulu-Natal[37], 69% in another study from Kenya[38], and 69% in another study from KwaZulu-Natal[39]. In contrast, the TPT completion rate in this study is lower than recent studies' completion rates across sub-Saharan Africa, which showed 46% in Namibia[36], 53% in Kenya[34], 58% in Tanzania[33], 75% in Malawi[23], 79% to 90% in KwaZulu-Natal[39], 83% in Uganda[5], and 88% in Nigeria[40]. The variation in the proportions of both TPT initiation and completion rates in this cohort compared to previous studies across South Africa can be attributed to several factors related to study designs, settings, criteria and definitions of TPT outcomes. For instance, in the study by Shenoi et al. in Msinga sub-district of KwaZulu-Natal province, where TPT completion was 90% in community-based referral (CBR) initiation and 79% among the clinic-initiated group, TPT completion was assessed through strict adherence check-ups using point-of-care (POC) urine tests for isoniazid metabolites in addition to medical record reviews[39]. Additionally, most of the previously mentioned studies primarily focused on IPT rather than shorter regimens. In comparison, this cohort's TPT initiation and completion were primarily based on medical chart reviews with follow-up data after the initiation of respective regimens, relying on the accuracy of data entry from medical chart to database entry.

5.1. Patient-level and systemic-level factors for TPT Initiation

Our study shows that both systemic-level (enrollment site) and patient-level (employment status) factors were strong predictors of TPT initiation. This finding is consistent with recent studies by Chandra et al., Fomundam et al., and Reddy et al., which highlight that TPT initiation varies across healthcare facilities and facility type is the main correlate for TPT initiation among PLHIV [35,37,41].

TPT initiation was higher in the rural clinic than in the peri-urban clinic (82% vs. 71%), with the rural clinic having a 21% higher adjusted likelihood of TPT initiation in our study. However, other studies showed that TPT initiation is influenced by numerous factors at both the patient and healthcare systemic levels. Systemic healthcare factors such as policy, logistic supply and readiness of TPT medication, provider-to-patient ratios, provider attitudes and knowledge about TPT, and the familiarity and utilization of guidelines play crucial role for TPT initiation. Previous studies have shown that provider attitudes and knowledge about TPT, particularly concerns about inducing isoniazid resistance due to poor patient adherence, contribute to reluctance to offer TPT, especially in South Africa where multi-drug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis rates are high[18,42–44]. Although the South African national guidelines for TPT interventions have been released, previous studies have shown that healthcare providers' familiarity and utilization of those guidelines significantly affect TPT initiation, with many prescribers finding them unclear, confusing, and ambiguous[18,42,43].

Another crucial systemic barrier influencing TPT initiation is the logistic supply and readiness of TPT medication, where shortages or insufficient supplies result in low TPT initiation and hinder implementation, especially in resource-limited settings[18,43–45]. This finding is evident in our study, where 7% of non-TPT initiation cases were recorded as being due to stockouts at clinics. The mentioned systemic-level and patient-level barriers to TPT initiation were also evident in our study, where 12% of patients switched from the 6H to the 3HP regimen after initiation during follow-up visits. We hypothesize that these regimen changes were possibly due to the availability of TPT regimens during follow-up visits for restart, or unfamiliarity with TPT guidelines by providers. However, further research is needed to explore the reasons for regimen changes from both patient and service provider perspectives, such as patient preferences and provider preferences regarding TPT regimens, logistic supply and availabilty of TPT regimens. Therefore, addressing systemic-level factors is essential for improving TPT initiation rates. This includes increasing resources to ensure a consistent supply of TPT medications, providing comprehensive training for healthcare providers to enhance their knowledge and attitudes toward TPT, and ensuring that guidelines are clear and effectively utilized. Additionally, improving the logistical

systems to prevent stockouts and ensuring that healthcare facilities are adequately staffed and equipped to manage TPT interventions will further support higher initiation rates.

Regarding patient-level factors, our study shows that employed participants had a 13% higher likelihood of TPT initiation compared to unemployed participants, which aligns with a study in Uganda by Oonyu et al., where employed participants were significantly associated with increased IPT uptake[46]. In addition, a study conducted by Baloyi et al., in the same setting highlights that socio-economic factors such as unemployment, unstable income, limited access to healthcare facilities due to travel costs, inflexible work schedules, and fear of crime when going to facilities situated in high-crime areas indirectly affect TPT uptake[18]. We hypothesize that, as evidenced by previous studies, employed participants were more likely to reach healthcare facilities and had better access, leading to higher TPT initiation rates compared to unemployed participants in our study settings. A study by Semitala et al. described that weekly clinic appointments posed significant barriers to TPT uptake and completion, as participants perceived them as costly in terms of transportation, time, childcare, and work absences[47]. Implementing less frequent follow-up visits and combining TPT initiation with ART initiation in a single clinic visit could potentially address these concerns and improve both TPT uptake and completion rates, which might be negatively affected by work conflicts and travel costs. Additionally, the health knowledge and perception of TPT benefits, influenced by the type of regimen and the quality of counseling provided by the clinic, play crucial roles in increasing TPT uptake. For instance, a study by Lester et al. showed that counseling was essential for patients, as many had not heard of IPT but were willing to take the medication after understanding that pill burden or socio-economic problems could be overcome through proper counseling[42]. Other factors, such as age, sex, marital status, education level, housing, smoking, alcohol consumption, CD4 count, and BMI, showed no association with TPT initiation in our study. These findings contrast with previous studies, which often indicated that TPT initiation was lower in older age groups compared to those aged under 25 years[41,48], and that individuals with secondary and higher education levels were more likely to begin TPT than those with no education[20,41]. Therefore, targeted support addressing patient-level factors associated with socio-economic barriers should be prioritized to improve TPT uptake. This

can be achieved by providing proper counseling to enhance patients' understanding of TPT benefits, offering shorter regimens, and implementing multi-month dispensing strategies to reduce the need for frequent follow-up visits. These measures can help mitigate issues such as pill burden, travel costs, and time off work, ultimately encouraging more patients to initiate and adhere to TPT.

5.2. Patient-level and systemic-level factors for TPT completion

Regarding TPT completion, participants initiating the 3HP regimen had a significantly higher completion rate (86%) compared to the 6H regimen (36%). In this cohort, the TPT regimen was the only strong predictor for TPT completion, with the 3HP regimen demonstrating a significantly lower risk of non-completion—more than half (58%)—compared to the 6H regimen. This finding is consistent with multiple previous studies that have highlighted shorter regimens as having better completion rates, up to two times higher, compared to the isoniazid monotherapy regimen of 6 to 9 months[4,15,49–51]. The findings from our study indicate that the shorter 3HP regimen has better completion rates compared to the isoniazid monotherapy 6H regimen, aligning with WHO recommendations[1,3]. Previous studies clearly show that shorter regimens are preferred due to their effectiveness, safety, and higher completion rates, as well as their generally lower risk of hepatotoxicity compared to longer isoniazid monotherapy[14,15,50]. Therefore, it is crucial to provide shorter regimens as a systemic-level factor to improve TPT completion in TB/HIV high-burden, resource-limited settings by enhancing adherence, reducing pill burden, minimizing hepatotoxicity, and decreasing the need for frequent clinic visits.

Our study shows a non-significant association between TPT completion and patient-level factors such as employment, education, age, and sex. Interestingly, we identified a clinically meaningful though not statistically significant association, indicating a 52% higher likelihood of TPT completion among unemployed participants compared to employed participants. This finding indirectly aligns with the study by Shayo et al., which highlighted that TPT non-completers were often PLHIV with higher socio-economic status[52]. However, it was not explained specifically since

it was a non-significant association. One possibility related to individual factors is that employed individuals had less flexibility to routinely attend medication pickups and appointments due to work conflicts, which could act as a barrier to clinic visits and refill visits, hindering treatment completion. The unemployed participants may have had an easier time adhering to the clinic visit schedule due to increased flexibility. However, further research is needed to explore these barriers, including transportation costs, distance to the clinic, and work schedules. One potential intervention to improve treatment completion could be to provide a full course of medication (e.g., 3 months of 3HP) at the initial prescription, instead of requiring patients to return monthly for refills, which could alleviate the challenges posed by work conflicts.

Similarly, participants with secondary education or higher showed a non-significant association with a 32% lower likelihood of TPT completion compared to those with only primary education. This is consistent with Shayo et al.'s findings, which indicated that non-completers were more likely to have secondary or post-secondary education[52]. A potential reason for our finding is the limited health knowledge regarding TPT benefits among higher-educated participants, leading to reduced adherence to clinical advice. This combined with skepticism or misinformation reducing motivation and competing life priorities, contributes to the issue. In this study, one participant with secondary education stopped TPT, thinking it was unnecessary to continue, which shows that higher education does not necessarily correlate with better adherence and health knowledge. However, further research is needed to explore these issues in depth, including patient-level health knowledge and perceptions of TPT benefits.

Additionally, our study found a non-significant association with age, where older participants had a higher risk of TPT non-completion compared to younger adults. This aligns with the findings of Ssendikwanawa et al., where PLHIV aged over 45 years had a significant association with TPT interruption[13]. It's interesting to note one possibility is that older people tend to have poor adherence due to forgetfulness, which impacts TPT completion[13]. We found that males had a 21% higher likelihood of TPT completion compared to females, which is inconsistent with other findings where females were up to two times more likely to complete TPT[19,39,53]. However, our

study did not find any significant associations between TPT completion and other factors such as enrollment sites (clinic), CD4 count, BMI, marital status, smoking, and alcohol consumption, which contrasts with previous findings. For instance, Amanya et al. found that being married was associated with increased TPT non-completion[53], and Oni et al. reported that smoking and alcohol consumption increased the risk of non-completion fourfold[22].

Our findings show non-significant associations with lower risk of TPT completion compared to their respective reference groups for certain sociodemographic factors, such as older age and being employed, which had borderline statistical significance, as well as having higher education and being female. One possible explanation from previous studies is that most PLHIV who appear healthy or show no signs of TB tend to interrupt or not take TPT due to limited health knowledge[13,54,55]. Another explanation is cultural stigma and norms related to TPT due to the interchangeable stigma of HIV and TB medications. A study by Boff et al. in KwaZulu-Natal found that the community perceived IPT as a toxin, believing it introduced dirt or "ukungcola" into the body due to causing foul body odor and strange urine smell[55]. Other factors that may influence TPT completion and require further research include pill burden, side effects, healthcare barriers like longer waiting times, lack of service privacy, and poor communication between service providers and patients.

Therefore, there may be some benefit in providing targeted support for people at higher risk of non-completion, such as health counseling focusing on the benefits of TPT while considering cultural norms, stigma, and socio-economic barriers. Additionally, providing shorter regimens over isoniazid monotherapy is crucial systemic-level factor for improving TPT completion among PLHIV in high TB/HIV burden, resource-limited settings.

6. Conclusion

Despite the rollout of WHO and national guidelines for TPT, implementation still faces multifaceted challenges related to patient-level and systemic-level barriers. Improving TPT coverage and outcomes is crucial to meet UNHLM and WHO recommendations for TB eradication. This study comprehensively described the TPT cascade of both initiation and completion in a high TB/HIV burden, resource-limited setting. The findings reveal significant gaps between initiation and completion rates that need to be addressed. Our study underscores the significance of offering shorter, patient-friendly regimens to enhance both TPT initiation and completion. The shorter regimen improves adherence, reduces pill burden, minimizes hepatotoxicity, and lessens the need for frequent clinic visits. Additionally, it is crucial to equip healthcare facilities with the necessary resources and training for effective TPT implementation. This includes maintaining a consistent supply of TPT medications, providing comprehensive training for healthcare providers to improve their knowledge and attitudes towards TPT, and ensuring that guidelines are clear and effectively utilized. Enhancing logistical systems to prevent stockouts and ensuring that healthcare facilities are adequately staffed and equipped to manage TPT interventions will further support higher initiation and completion rates. Overall, this study provides valuable insights into the multifaceted barriers to TPT initiation and completion, emphasizing the need for integrated strategies that address both patient-level and systemic-level factors to achieve better health outcomes for PLHIV. Addressing these barriers will be pivotal in reaching global targets for TB prevention and ultimately eradicating the disease in high-burden settings.

7. Supplemental materials

Table 5: Unadjusted model sensitivity analysis for TPT regimen changed participants with missing follow up data by imputing completion status and comparison to final model results

		Final unadjusted model			Sensitivity analysis of imputed completion status "No"			Sensitivity analysis of imputed completion status "Yes"		
Variables	Category	N = 241 n/N[1]	RR[3]	95% CI[2]	N = 260 n/N[1]	RR[3]	95% CI[2]	N = 260 n/N[1]	RR[3]	95% CI[2]
Sex	*Female (ref)*	64/150			64/162			76/162		
	Male	38/91	1.22	0.78, 1.90	38/98	1.05	0.64, 1.72	45/98	1.17	0.80, 1.71
Age category	*< 30 years (ref)*	45/91			45/98			52/98		
	30-50 years	54/136	0.84	0.60, 1.18	54/148	0.78	0.55, 1.11	66/148	0.86	0.65, 1.14
	>50 years	3/14	0.35	0.11, 1.07	3/14	0.37	0.12, 1.09	3/14	0.36	0.12, 1.08
CD4 category	*<200 cell/mm³ (ref)*	25/59			25/65			31/65		
	200-500 cell/mm³	43/100	1.04	0.72, 1.48	43/111	1.01	0.69, 1.49	54/111	1.03	0.77, 1.36
	>500 cell/mm³	33/79	1.05	0.70, 1.57	33/81	1.08	0.71, 1.64	35/81	1.04	0.74, 1.47
	Missing	3			3			3		
BMI category	*Normal weight (ref)*	57/132			57/142			67/142		
	Overweight	36/90	1.00	0.75, 1.33	36/97	0.93	0.69, 1.25	43/97	1.00	0.77, 1.30
	Underweight	9/19	0.80	0.51, 1.24	9/21	0.90	0.53, 1.49	11/21	0.83	0.57, 1.19
Housing type	*Formal housing / Apartment (ref)*	79/193			79/205			91/205		
	Informal housing	1/2	1.13	0.20, 6.31	1/3	0.66	0.10, 4.54	2/3	1.10	0.42, 2.78
	Traditional / RDP housing	21/43	1.10	0.77, 1.55	21/49	1.03	0.69, 1.53	27/49	1.10	0.83, 1.44
	Missing	3			3			3		
Education level	*Primary (ref)*	13/30			13/31			14/31		
	Secondary and above	86/202	0.69	0.42, 1.15	86/220	0.71	0.43, 1.17	104/220	0.69	0.44, 1.09
	Unknown	3/9	0.74	0.29, 1.90	3/9	0.75	0.29, 1.94	3/9	0.74	0.30, 1.83
Employment	*Employed (ref)*	28/80			27/91			32/91		
	Unemployed	76/144	1.50	0.94, 2.39	75/169	1.49	0.93, 2.38	89/169	1.43	0.97, 2.10
Enrollment sites	*Peri-urban clinic (ref)*	56/143			62/161			76/161		
	Rural clinic	48/90	0.92	0.66, 1.29	40/99	1.02	0.72, 1.46	45/99	0.91	0.69, 1.21
Smoking status	*No (ref)*	74/181			74/196			89/196		
	Yes	28/60	1.05	0.73, 1.51	28/64	1.17	0.79, 1.72	32/64	1.08	0.78, 1.48
Alcohol consumption	*No (ref)*	52/118			52/129			63/129		
	Yes	50/123	0.95	0.68, 1.33	50/131	0.97	0.70, 1.41	58/131	0.94	0.71, 1.21
Final TPT regimen[4]	*3HP (ref)*	25/29			25/48			44/48		
	IPT (6H)	77/212	0.41	**0.29, 0.60****	77/212	0.71	0.41, 1.23	77/212	0.40	**0.30, 0.54****

[1] *n (completed - Yes) / N (overall)*
[2] *95% Confidence interval*
[3] *Risk ratio*
[4] *TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive , 6H = 6 months of daily isoniazid*

** *p-value <0.001*

Table 6: Adjusted model sensitivity analysis for TPT regimen changed participants with missing follow up data by imputing completion status and comparison to final model results

		Final adjusted model			Sensitivity analysis of imputed completion status "No"			Sensitivity analysis of imputed completion status "Yes"		
Variables	Category	N = 241 n/N[1]	aRR[3]	95% CI[2]	N = 260 n/N[1]	aRR[3]	95% CI[2]	N = 260 n/N[1]	aRR[3]	95% CI[2]
Sex	*Female (ref)*	64/150			64/162			76/162		
	Male	38/91	1.21	0.78, 1.88	38/98	1.10	0.65, 1.77	45/98	1.18	0.80, 1.72
Age category	*< 30 years (ref)*	45/91			45/98			52/98		
	30-50 years	54/136	0.85	0.60, 1.19	54/148	0.79	0.56, 1.12	66/148	0.87	0.66, 1.15
	>50 years	3/14	0.36	0.12, 1.10	3/14	0.39	0.13, 1.14	3/14	0.36	0.12, 1.10
CD4 category	*<200 cell/mm³ (ref)*	25/59			25/65			31/65		
	200-500 cell/mm³	43/100	1.01	0.71, 1.43	43/111	0.99	0.68, 1.44	54/111	1.05	0.77, 1.34
	>500 cell/mm³	33/79	1.03	0.70, 1.53	33/81	1.10	0.71, 1.58	35/81	1.03	0.74, 1.45
	Missing	3			3			3		
BMI category	*Normal weight (ref)*	57/132			57/142			67/142		
	Overweight	36/90	1.00	0.75, 1.35	36/97	0.93	0.70, 1.26	43/97	1.01	0.77, 1.32
	Underweight	9/19	0.81	0.52, 1.26	9/21	0.88	0.53, 1.47	11/21	0.83	0.57, 1.20
Housing type	*Formal housing / Apartment (ref)*	79/193			79/205			91/205		
	Informal housing	1/2	1.21	0.25, 5.88	1/3	0.66	0.10, 4.41	2/3	1.08	0.43, 2.68
	Traditional / RDP housing	21/43	1.09	0.78, 1.54	21/49	1.03	0.70, 1.54	27/49	1.08	0.82, 1.42
	Missing	3			3			3		
Education level	*Primary (ref)*	13/30			13/31			14/31		
	Secondary and above	86/202	0.68	0.43, 1.09	86/220	0.72	0.45, 1.13	104/220	0.68	0.45, 1.03
	Unknown	3/9	0.76	0.30, 1.90	3/9	0.80	0.30, 1.92	3/9	0.74	0.31, 1.81
Employment	*Employed (ref)*	28/80			27/91			32/91		
	Unemployed	76/144	1.52	0.97, 2.38	75/169	1.47	0.95, 2.30	89/169	1.45	0.10, 2.11
Enrollment sites	*Peri-urban clinic (ref)*	56/143			62/161			76/161		
	Rural clinic	48/90	0.91	0.65, 1.28	40/99	1.02	0.71, 1.46	45/99	0.90	0.68, 1.21
Smoking status	*No (ref)*	74/181			74/196			89/196		
	Yes	28/60	1.10	0.74, 1.52	28/64	1.15	0.78, 1.70	32/64	1.07	0.78, 1.47
Alcohol consumption	*No (ref)*	52/118			52/129			63/129		
	Yes	50/123	0.94	0.68, 1.31	50/131	1.00	0.66, 1.38	58/131	0.94	0.71, 1.25
Final TPT regimen[4]	*3HP (ref)*	25/29			25/48			44/48		
	IPT (6H)	77/212	0.42	**0.29, 0.60****	77/212	0.71	0.41, 1.24	77/212	0.40	**0.30, 0.54****

[1] *n (completed - Yes) / N (overall)*
[2] *95% Confidence interval*
[3] *adjusted Risk ratio*
[4] *TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive , 6H = 6 months of daily isoniazid*

** *p-value <0.001*

Table 7: Comparative analysis of Unadjusted and three Adjusted models based on Performance Metrics and multicollinearity scores for TPT Completion analysis among TPT Initiated Participants

			Full model (unadjusted)		Model 1[a]		Model 2[b]		Model 3[c]		Average VIF score[d]	
Variables	**Category**	**N = 241 n/N[1]**	**RR[3]**	**95% CI[2]**	**aRR[4]**	**95% CI[2]**	**aRR[4]**	**95% CI[2]**	**aRR[4]**	**95% CI[2]**	**GVIF[5]**	**aGVIF[6]**
Sex	*Female (ref)*	64/150									2.00	1.42
	Male	38/91	1.22	0.78, 1.90	1.21	0.78, 1.88	1.26	0.81, 1.96	1.22	0.78, 1.90		
Age category	*< 30 years (ref)*	45/91									1.56	1.12
	30-50 years	54/136	0.84	0.60, 1.18	0.85	0.60, 1.19	0.87	0.62, 1.20	0.84	0.60, 1.18		
	>50 years	3/14	0.35	0.11, 1.07	0.36	0.12, 1.10	0.37	0.12, 1.12	0.35	0.11, 1.07		
CD4 category	*<200 cell/mm³ (ref)*	25/59									1.28	1.06
	200-500 cell/mm³	43/100	1.04	0.72, 1.48	1.01	0.71, 1.43	1.03	0.72, 1.47	1.04	0.72, 1.48		
	>500 cell/mm³	33/79	1.05	0.70, 1.57	1.03	0.70, 1.53	1.04	0.71, 1.52	1.05	0.70, 1.57		
	Missing	3										
BMI category	*Normal weight (ref)*	57/132									1.37	1.08
	Overweight	36/90	1.00	0.75, 1.33	1.00	0.75, 1.35	1.01	0.75, 1.35	1.00	0.75, 1.33		
	Underweight	9/19	0.80	0.51, 1.24	0.81	0.52, 1.26	0.81	0.52, 1.28	0.80	0.51, 1.24		
Housing type	*Formal housing / Apartment (ref)*	79/193									1.24	1.06
	Informal housing	1/2	1.13	0.20, 6.31	1.21	0.25, 5.88			1.13	0.20, 6.31		
	Traditional / RDP housing	21/43	1.10	0.77, 1.55	1.09	0.78, 1.54			1.09	0.76, 1.54		
	Missing	3										
Education level	*Primary (ref)*	13/30									1.48	1.10
	Secondary and above	86/202	0.69	0.42, 1.15	0.68	0.43, 1.09	0.67	0.43, 1.04	0.69	0.42, 1.14		
	Unknown	3/9	0.74	0.29, 1.90	0.76	0.30, 1.90	0.74	0.29, 1.86	0.75	0.28, 1.90		
Employment	*Employed (ref)*	28/80									1.33	1.16
	Unemployed	76/144	1.50	0.94, 2.39	1.52	0.97, 2.38	1.52	0.98, 2.36	1.50	0.94, 2.38		
Enrollment sites	*Peri-urban clinic (ref)*	56/143									1.22	1.10
	Rural clinic	48/90	0.92	0.66, 1.29	0.91	0.65, 1.28	0.91	0.65, 1.28	0.92	0.65, 1.28		
Smoking status	*No (ref)*	74/181									1.61	1.27
	Yes	28/60	1.05	0.73, 1.51	1.10	0.74, 1.52	1.01	0.70, 1.48	1.05	0.73, 1.51		
Alcohol consumption	*No (ref)*	52/118									1.24	1.11
	Yes	50/123	0.95	0.68, 1.33	0.94	0.68, 1.31	0.94	0.67, 1.30	0.94	0.68, 1.33		
Final TPT regimen[7]	*3HP (ref)*	25/29									1.19	1.09
	IPT (6H)	77/212	0.41	**0.29, 0.60****	0.42	**0.29, 0.60****	0.42	**0.29, 0.59****	0.41	**0.28, 0.60****		
Model performance metrics (Adjusted R^2: the adjusted R^2 values for each model. AIC: the Akaike Information Criterion values for each model)				**Adjusted R^2 = - 0.002042008** AIC = 388.9343		**Adjusted R^2 = 0.005960352** AIC = 385.3552		**Adjusted R^2 = 0.002922547** AIC = 385.9487		**Adjusted R^2 = -0.00204201** AIC = 388.9342		

*[a] Model 1 = adjusted for Sex, Age, Employment, Education, enrollment sites and housing types (*final model)*
*[b] Model 2 = adjusted for Sex, Age, Employment, Education, and enrollment sites (*removing housing types from model 1)*
*[c] Model 3 = adjusted for Sex, Age, Employment, Education, enrollment sites, housing types and marital status (*adding marital status to model 1)*

[1] n (completed - Yes) / N (overall)
[2] 95% Confidence interval
[3] Risk ratio
[4] adjusted Risk ratio

[d] Average Variance Inflation Factor (VIF) across all models
[5] Generalized Variance Inflation Factor (GVIF)
*[6] Adjusted Generalized Variance Inflation Factor (aGVIF) = GVIF^(1/(2*df))*

[7] TPT = Tuberculosis Preventive Therapy, 3HP = 3 months of once-weekly rifapentine and isoniazid, IPT = Isoniazid Preventive Treatment , 6H = 6 months of daily isoniazid

*** p-value <0.001*

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