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Risk factors for recurrent tuberculosis among HIV patients who are on anti-retroviral treatment in rural northeast, South Africa

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RISK FACTORS FOR RECURRENT TUBERCULOSIS AMONG HIV PATIENTS WHO ARE ON ANTI-RETROVIRAL TREATMENT IN RURAL NORTHEAST, SOUTH AFRICA

By

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A Research Report submitted to the Faculty of Health Sciences, University of Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology in the Field of Implementation Sciences

Supervisors: Prof. Latifat Ibisomi and Dr. Chodziwadziwa Kabudula

February, 2024.

DECLARATION

I, Kingsley Kanzoole, declare that this research report is my own unaided work. It is being submitted in partial fulfilment of the requirement for the degree of Master of Science (MSc) in Epidemiology (Field of Implementation Science) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



5th day of February, 2024.

DEDICATION

I dedicate this work to my family, particularly the young ones, this is for you, that, “it is possible”.

DEFINITIONS OF TERMS

Tuberculosis: Tuberculosis is a chronic infectious disease caused by the bacterium Mycobacterium tuberculosis (1). It primarily affects the lungs but can also affect other parts of the body such as the brain, kidneys, and bones (1).

Recurrent Tuberculosis: another episode of tuberculosis disease among patients who were successfully treated for TB and declared cured (2) . In this research, recurrent tuberculosis means another tuberculosis diagnosis after one year of treatment completion of the initial tuberculosis episode.

Patients: Patients are sick people who are receiving medical treatment from a doctor or hospital. In this research, "patients" means all participants that were diagnosed with Human Immunodeficiency Virus and tuberculosis within the study period.

Poor tuberculosis treatment adherence: Refers to a situation where a patient with tuberculosis does not follow the recommended treatment plan as prescribed by their healthcare provider. This can include missing doses of medication, interrupting treatment before the recommended duration, or not completing the full course of treatment. In this study, "poor tuberculosis treatment adherence" means missing clinic appointment for drug refill for 60 days or more than 60 days (2,3).

Poor HIV treatment adherence: Poor HIV treatment adherence refers to a situation where a patient with HIV does not follow the recommended treatment plan as prescribed by their healthcare provider. This can include missing doses of medication, interrupting treatment before the recommended duration, or not completing the full course of treatment. In this study, "poor HIV treatment adherence" means missing clinic appointment for drug refill for 60 days or more than 60 days (2,3).

ABSTRACT

Background: Tuberculosis (TB) is a major public health concern, and according to the World Health Organization (WHO), is one of the top 10 causes of death worldwide. Recurrent TB is a significant contributor to the overall TB burden worldwide, particularly in areas where TB prevalence is high (4–6), and among HIV infected people.

Aim: In this study, we investigated the risk-factors that are associated with the recurrence of TB among HIV infected people in rural northeast, South Africa.

Methods: The study employed a retrospective cohort study design and used data from Agincourt health socio-demographic surveillance system spanning from 1st January 2014 to 31st December 2022. Data analysis was conducted using STATA 17 SE as the analytical tool. Cox regression was used to determine risk factors for recurrent TB among HIV patients on ART in rural northeast, South Africa.

Results: The study included 4,803 participants with 1,326 (27.6%) males and 3,477 females (72.4%). The participants were predominantly of HIV WHO Stage 1 (84.7%), followed by Stage 2 (7.6%), then Stage 3 (7.0%) and Stage 4 (0.7). The age distribution had 24.8% aged 18-29, 34.5% aged 30-39, 23.1% aged 40-49, 11.0% aged 50-59 and 6.6% aged 60 and above. The study population had a CD4 count median of 229 cells/mm3 with an IQR of 112-390 cells/mm3 and a median duration of previous TB treatment of 31 weeks with an IQR of 16-49 weeks. Out of the 4,803 patients, 396 (8.2%) experienced recurrent TB. This translated to a recurrence rate of 3.0 per 100 person years. The median time to TB recurrence was 1.93 years, with approximately 50% experiencing the recurrence within this period. The significant risk factors associated with recurrent TB were being male (AHR=1.48, CI: 1.11 – 1.96), WHO HIV stage (AHR=2.53, CI: 1.81 – 3.54), baseline CD4 count (AHR=0.98, CI: 0.98 – 0.99), and duration of previous TB treatment (AHR=0.96, CI: 0.93 – 0.98).

Conclusion: This study has identified significant risk factors for recurrent TB among HIV patients in rural northeast South Africa. Male patients have a higher risk, necessitating targeted interventions. Advanced HIV stages increase recurrence risk, emphasizing early diagnosis and management. Maintaining higher CD4 counts and continuous monitoring during and after TB treatment are vital to reducing recurrence. These findings inform strategies to improve health outcomes and control recurrent TB among HIV patients receiving ART in the region.

Keywords: Recurrent tuberculosis, Recurrence rate, ART, HIV, Incidence rate

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"If I have seen further, it is by standing on the shoulders of giants." – Sir Isaac Newton.

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TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
DEFINITIONS OF TERMS iv
ABSTRACT v
ACKNOWLEDGEMENTS vi
LIST OF FIGURES ix
ABBREVIATIONS AND ACRONYMS ix
CHAPTER 1 1
1 Introduction 1
1.1 Background 1
1.2 Problem Statement 3
1.3 Justification of the Study 4
1.4 Research Question 5
1.5 Aim 5
1.6 Objectives 5
1.7 Literature Review 6
1.7.1 Incidence rate of recurrent TB in HIV patients 6
1.7.2 Time to recurrent TB after Initial TB Treatment 7
1.7.3 Factors associated with the recurrence of TB 8
1.7.4 Conceptual Framework 13
CHAPTER 2 15
2 Methods 15
2.1 Study Site 15
2.2 Study Design 16
2.3 Study Population 17
2.4 Power Calculation 19
2.5 Data Source 16
2.6 Data Management 19
2.6.1 Outcome variable: recurrent TB 19
2.6.2 Explanatory variables 19
2.7 Statistical analysis 23
2.8 Study Limitations 24
2.9 Ethical Consideration 24
CHAPTER 3 25
3 Results 25
3.1 Sample Characteristics 25

3.2 Incidence rate of recurrent TB among HIV patients who are on ART in rural northeast 28
3.3 Time to another TB episode after successful treatment 30
3.4 Risk factors for recurrent TB among HIV patients who are on ART in rural northeast 36
CHAPTER 4 39
4 Discussion 39
4.1 The incidence rate of recurrent TB among HIV patients on ART 39
4.2 Time to another TB episode after successful treatment 40
4.3 Risk factors for recurrent TB among HIV patients on ART 42
4.4 Strengths and Limitations 43
CHAPTER 5 45
5 Conclusion and Recommendations 45
5.1 Conclusion 45
5.2 Recommendations 45
5.3 Funding Acknowledgement 47
References: 48
Appendices 54

LIST OF FIGURES

Figure 1.1: Conceptual Framework showing factors associated with TB recurrence 14
Figure 2.1: Map of research area 15
Figure 2.2: Flow Chart showing how participants were selected for analysis.....18
Figure 3.1: Risk of TB recurrence over time 30
Figure 3.2: Risk of TB recurrence over time, stratified by sex.....31
Figure 3.3: Risk of TB recurrence over time, stratified by WHO stages of HIV 32
Figure 3.4: Risk of TB recurrence over time, stratified by comorbidities.....33
Figure 3.5: Risk of TB recurrence over time, stratified by TB treatment adherence 34
Figure 3.6: Risk of TB recurrence over time, stratified by HIV treatment adherence 35

LIST OF TABLES

Table 2.1: Variables of Interest in the study.....21
Table 3.1: Characteristics of the participants.....27
Table 3.2: Tuberculosis recurrent rates by various variables 29
Table 3.3: Risk factors associated with recurrent tuberculosis.....38

ABBREVIATIONS AND ACRONYMS

AHR	**-**	Adjusted Hazard Ratio
HDSS	**-**	Health Demographic Surveillance System
HIV	-	Human Immunodeficiency Virus
HR	**-**	Hazard Ratio
MDR-TB	-	Multi-drug resistant TB
NTSS	-	United States National Tuberculosis Surveillance System
PY	-	Person-Years
TB	-	Tuberculosis
TDR	-	Tropical Disease Research
UNDP	-	United Nations Development Programme
UNICEF	-	United Nations International Children's Emergency Fund
WHO	-	World Health Organisation
XDR-TB	-	Extensive drug resistant TB

CHAPTER 1

1 Introduction

This chapter provides an overview of recurrent tuberculosis in South Africa and the scope of the issue. The conceptual framework and the factors connected to recurrent TB are explored. The chapter is divided into the following subsections: background; literature review; problem statement; study rationale; research question; aim; objectives; and conceptual framework.

1.1 Background

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium Mycobacterium tuberculosis (1). Although it mostly affects the lungs, it can also affect other organs such as the brain, kidneys, and bones (1). According to the World Health Organisation, TB is one of the top 10 global causes of mortality, raising serious public health concerns (1). In 2020, an estimated 10 million people were diagnosed with TB and 1.5 million died from the disease (1).

Recurrent tuberculosis (TB) is defined by the World Health Organization as another episode of TB disease among patients who were successfully treated for TB and declared cured (2). Recurrent TB, which can result from endogenous reactivation of a pre-existing infection or exogenous reinfection by a new strain (2,4) is also defined by the US National Tuberculosis Surveillance System (NTSS) as TB diagnosis that occurs twelve months or more after the last clinical encounter for anti-tuberculosis treatment, any TB diagnosis that occurs sooner than twelve months is considered a continuation of the same episode and not counted as a new incident of TB (4).

Recurrent tuberculosis is a significant contributor to the overall TB burden worldwide, particularly in areas where TB prevalence is high (5–7), and among HIV infected people (7–9). Previous research has shown a strong correlation between TB and HIV epidemics, as individuals with HIV have a higher risk of contracting TB again, making them more vulnerable to recurrent TB disease (8,10–12). According to various studies, recurrent TB accounts for 5 to 30 percent of the global TB burden (5,7,9,10).

South Africa is one of the countries with a high burden of TB, accounting for three percent of cases worldwide (1,13). According to Fischinger et al. (2021), the majority of TB cases in South Africa are recurrent cases, caused by relapse or reinfection (14). Recent studies indicate that recurrent TB accounts for a significant proportion of the overall TB burden in the country, with estimates ranging from 8% to 20% of all TB cases (5,13) . The incidence of recurrent TB in South Africa is high, with one recent study in Cape town showing an incidence rate of 16.4 per 1000 person-years (5).

The significant burden of recurrent TB in South Africa emphasizes the urgent need for targeted interventions and strategies to address this issue. The high incidence of recurrent TB, particularly among individuals with HIV, poses challenges to TB control efforts and hinders the progress made in reducing the overall TB burden. Identifying the risk factors associated with recurrent TB and implementing appropriate interventions is crucial for developing effective prevention and treatment approaches and can enable South Africa make significant strides in reducing the burden of TB and improving the overall health outcomes of its population.

1.2 Problem Statement

Despite the advances in controlling TB in South Africa, the epidemic continues to be one of the major causes of death in the country (1). The situation is further exacerbated by the persistent issue of TB recurrence, which has significant implications for TB control efforts (15). Recurrent tuberculosis poses a significant challenge to global tuberculosis control programs because it is often associated with the emergence of drug-resistance strains, which further complicates treatment and reduces successful outcomes (1,15,16). The social and economic impact of recurrent TB is profound, leading to prolonged illness, increased healthcare costs, and productivity loss (17).

In areas with high TB prevalence, such as rural northeast, South Africa, the comorbidity of TB and HIV has been found to play a significant role in the cases of recurrent TB. In 2016, the HIV prevalence rate in this region was the second highest in the country, reaching 15.2% (18). This alarming statistic highlights the interconnectedness between TB and HIV, with each disease exacerbating the risk and severity of the other. Moreover, TB was the primary cause of mortality in rural northeast, South Africa accounting for 7.9% of deaths in 2015 (19). The recurrence of TB not only poses a threat to the health and well-being of individuals but also increases the potential for transmission within communities, particularly among individuals living with HIV/AIDS (20).

To effectively reduce the spread of recurrent TB and mitigate the incidence of multi-drug resistant TB (MDR-TB), it is imperative to identify the factors associated with repeated episodes of TB. By identifying the underlying causes and risk factors contributing to TB recurrence, targeted interventions and strategies can be developed to address the unique challenges faced by this population.

1.3 Justification of the Study

There is a global concern about TB recurrence in patients that were successfully treated for TB, especially its role in multi-drug resistant TB (1). Recurrent TB not only poses a significant challenge to individual health but also undermines the efforts of tuberculosis control programs worldwide. The emergence of multi-drug resistant strains as a result of TB recurrence further compounds the problem, as treatment options become limited and less effective (15).

The occurrence of recurrent TB in rural northeast, South Africa poses a serious threat to public health as it undermines the progress made in TB control efforts. Patients who experience recurrent TB face prolonged illness, increased healthcare costs, and potentially adverse treatment outcomes (1).

Furthermore, the impact of recurrent TB extends beyond the individual patient, impacting the community at large. The potential transmission of drug-resistant TB strains in the community poses a public health risk, as it increases the likelihood of further treatment failures and challenges the control of TB transmission. Addressing the problem of recurrent TB in rural northeast, South Africa is crucial for improving individual health outcomes, reducing the burden of drug-resistant TB, and safeguarding the health and well-being of the entire community.

1.4 Public Health Implications of the Study

Recurrent TB is one of the public health problems in South Africa. It is one of the major causes of mortality among HIV patients in South Africa (1). Thus, unravelling the risk factors for recurrence of TB among the HIV population can inform policy makers on interventions that can curb the problem.

1.5 Research Question

What are the risk factors for the recurrence of tuberculosis after successful treatment among HIV patients who are on anti-retroviral treatment in rural northeast, South Africa?

1.6 Aim

To determine the risk factors for the recurrence of tuberculosis in HIV patients who are on anti-retroviral treatment in rural northeast, South Africa.

1.7 Objectives

1. To determine the incidence rate of recurrent TB among HIV patients who are on ART in rural northeast, South Africa
2. To determine the time to another TB episode after successful TB treatment in HIV patients who are on ART in rural northeast, South Africa
3. To identify risk factors for TB recurrence after successful treatment among HIV patients who are on ART in rural northeast, South Africa

1.8 Literature Review

The literature review was conducted through searching "recurrent tuberculosis in HIV patients", "factors associated with recurrent tuberculosis", "time to another tuberculosis episode after initial treatment" on PubMed, Google Scholar, and Scopus.

1.8.1 Incidence rate of recurrent TB in HIV patients

HIV infection increases the risk of TB recurrence due to its impact on the immune system (10). Studies have shown that TB recurrence is considerably high in HIV-infected people (8,12). The HIV epidemic has contributed to a high incidence of TB and increased the risk of TB recurrence among those who have already been treated (5,7).

One South African study showed that TB recurrence was nearly four times as prevalent among South African gold miners who were HIV-positive, with incidence rates of 8.2 per 100 person-years in men with HIV infection and 2.2 per 100 person-years in men without HIV (IRR 3.7, 95% CI 2.4-5.7) (12). A study conducted by Fischinger et al. (2021) in South Africa showed that people with HIV were more likely to develop recurrent TB within the first year of completing treatment and that this increased risk persisted up to five years after treatment completion (14).

Another South African study showed that the probability of reactivating latent TB disease among HIV-uninfected people is about 10% during their lifetime, but the risk rises to almost 10% per year in those living with HIV (8). The study also showed that co-infection with HIV carries a significant risk of TB recurrence (8).

In addition to South Africa, other countries across the globe have also reported significant rates of TB recurrence among HIV-infected individuals. In Kenya, Hawken et al. (1993) observed that the recurrence incidence of tuberculosis was 34 times higher in 58 HIV-1-positive patients than in 138 HIV-1-negative patients (adjusted rate ratio 33.8, 95% CI 4.3-264) (11).

Similarly, studies conducted in other countries such as Brazil and Malawi have revealed substantial rates of TB recurrence among HIV-infected individuals (21–23). In Brazil, the incidence rate of recurrent TB in people living with HIV was estimated to be around 9 per 100 person-years (22). According to a study conducted in Malawi, people with HIV experience recurrent TB at an incidence rate of 2.2 per 100 person-years, compared to 0.4 per 100 person-years for people without HIV (23).

A systematic review and meta-analysis on recurrent TB by Vega et al. (2021), found an incidence rate of 2.26 per 100 person-years at risk, with HIV infection as a major contributor to the recurrence of TB (based on 145 studies) (7).

1.8.2 Time to recurrent TB after Initial TB Treatment

Previous studies have shown that recurrent TB often occurs within two years after treatment completion, with a peak incidence within the first six months (9,24). The median time to another TB episode was found to be 21 months in a study by Florian M. Marx et al. (2014) that looked at tuberculosis recurrence patterns in a high burden setting and focused on the interval between the end of treatment and recurrent disease in Cape Town, South Africa. The interquartile range for this time was 8 to 48 months (25). Another study by Qiao-ling Ruan et al. (2022) in China looked at longitudinal data on pulmonary tuberculosis recurrence rates and risk factors for recurrence among successfully treated smear-positive tuberculosis cases. It was discovered that 4.9% of cases had recurrent TB within a median observation period of 1565 days (4.3 years), with 51.1% of recurrences taking place within the first year (26).

Additional studies have further supported the findings regarding the timing and incidence of recurrent TB after treatment completion. A retrospective cohort study by Moosazadeh et. al. (2015) focusing on predictors of tuberculosis recurrence in smear-positive TB patients in Iran, diagnosed between 2002 and 2011, found a recurrence incidence of 8.3% among 1,271 eligible participants, with 85.9% of recurrences occurring within 1-5 years after successful treatment (27).

A systematic review and meta-analysis of 25 studies found that the overall recurrence rate of TB was 6.2% within the first two years after treatment completion (28). The highest risk of recurrence was observed within the first six months, with a cumulative incidence of 2.3% (28). The risk of recurrence decreased gradually over time, with a cumulative incidence of 4.7% at one year and 5.6% at two years (28).

1.8.3 Factors associated with the recurrence of TB

Recurrence of TB can be caused by a variety of factors. This section focuses on literature that aimed to identify the factors that are associated with the recurrence of TB, with a focus on patient's immunological state, demographics, and treatment-related factors. Studies have shown that poor treatment adherence, patient's immunological state (diabetes comorbidity, CD4 count, and viral load), age differences, sex differences, resistance to TB medication, the genotype of the strains, malnutrition, and smoking are some of the factors that can contribute to the recurrence of TB (9,20,29). Investigating the factors associated with the recurrence of TB is crucial for developing effective strategies to prevent and manage the disease.

1.8.3.1 Age

Age has been found to be a significant risk factor for recurrent TB in previous studies (6,26). A study conducted in South Africa analysed the risk factors for recurrent tuberculosis and found that younger age was associated with an increased risk of recurrence, with a median age of 35 years (6). Another study found that older age was associated with an increased risk of TB recurrence, with 60 years and older being at higher risk (26). In contrast, a systematic review of published literature on factors linked to tuberculosis recurrence among people living with HIV in Africa, found that age was not significantly associated with recurrent TB (10). These contrasting findings highlight the importance of considering age as a factor for recurrent TB in specific contexts.

1.8.3.2 Diabetes comorbidity

A study by Pin-Hui Lee et al. (2014) which aimed at investigating the relationship between diabetes mellitus and TB recurrence in Taiwan, showed that diabetes during previous TB treatment was a risk factor for the recurrence of TB, with patients who were diabetic being almost two times more prone to recurrent TB than individuals without diabetes (OR: 1.96, 95% CI: 1.22–3.15) (30). Another study that explored the intersection of diabetes and tuberculosis was conducted by Dooley et al. (2016) in South Africa. The research focused on the impact of diabetes on TB treatment outcomes. The study found that TB patients with comorbid diabetes experienced a higher risk of unfavourable treatment outcomes, such as treatment failure, recurrence of TB, and death, compared to TB patients without diabetes. The adjusted hazard ratio (AHR) for unfavourable treatment outcomes in the presence of diabetes was 1.74 (95% CI: 1.48–2.05) (31).

A meta-analysis by Jeon et al. (2018) aimed at comprehensively evaluating the association between diabetes and TB risk globally. This study pooled data from various countries and found a significant positive association between diabetes and the risk of developing active TB. According to the meta-analysis, those with diabetes had a 3-fold higher chance of developing tuberculosis (TB) and having it return than people without diabetes (pooled relative risk = 3.11, 95% CI: 2.37– 4.09) (32).

1.8.3.3 Sex

Studies have shown that sex is one of the factors that is associated with the recurrence of TB (26,27). A study by Qiao-ling Ruan et. al. (2022), in China, found that being male was associated with an increased risk of TB recurrence, with the adjusted hazard ratio (AHR) of 1.61 (95%CI 1.30-2.00) (26). In a different study by Hin Moi Youn et. al. (2022), sex was also found to be a significant predictor of recurrent TB, with the recurrence rate being higher in men than women (AHR = 1.81, at a 95% CI, range: 1.11–2.94) (33). This sex disparity in TB recurrence may be related to differences in healthcare-seeking behaviour. For example, studies have shown that women tend to seek healthcare earlier and more frequently than men, which may lead to earlier detection and treatment of TB infection and lower rates of recurrence (34).

1.8.3.4 CD4 count

Moodley et al. (2015) conducted a systematic review to identify the factors linked to TB recurrence among individuals in Africa who are infected with HIV. According to their findings, some of the significant factors associated with the recurrence of TB in this population include the baseline CD4 count and the HIV viral load (10). A study conducted by Punjabi et al. (2007), which evaluated the risk factors for TB recurrence among HIV-positive and HIV-negative individuals, showed that TB recurrence was significantly higher among people with HIV infection (6.7%, 95% CI 5.9-7.6) compared to people without HIV infection (3.3%, 95% CI 2.8-3.9) (24). The study also showed that in the group of individuals with HIV infection, the recurrence of TB was linked to having a low CD4 count. (24).

1.8.3.5 WHO stage of HIV

Several studies have explored the relationship between WHO staging for HIV and the risk of recurrent TB, providing valuable insights into this complex interplay. Findings from these studies suggest that advanced HIV disease, as indicated by higher WHO stages, is associated with an increased risk of TB recurrence (35–37).

A study conducted by Lawn et. al. (2005), which aimed to determine the long-term incidence of tuberculosis and associated risk factors among individuals receiving HAART in South Africa, demonstrated a significantly higher incidence of recurrent TB among HIV-infected individuals in advanced WHO stages compared to those in earlier stages, with those at WHO stage 3 or stage 4 having about 3.6 time more likely to experience recurrent TB as compared to those on stage 1 or stage 2 (ARR, 3.60; 95% CI, 1.32–9.80) (35).

Similarly, a study conducted by Mohammed et. al. (2015), in Ethiopia, on tuberculosis among HIV-positive patients, showed that, as the WHO stage advanced, the incidence of recurrent TB increased, with those at stage 3 or stage 4 at a high risk (OR=4.12) (37).
These findings emphasize the importance of monitoring WHO staging as a predictor of TB recurrence among individuals living with HIV.

1.8.3.6 Poor adherence to TB and or HIV medication

Previous studies have shown that poor adherence to tuberculosis medication is associated with TB recurrence (38–41). A study by Jessica et al. (2018), which aimed to investigate the risk factors for developing recurrent tuberculosis (TB) among patients who had completed treatment for smear-positive pulmonary TB in high-prevalence settings in Vietnam, showed that patients with poor adherence to TB medication had a high likelihood of experiencing recurrent TB (42). In addition, the study also found that HIV co-infection further complicates the management of TB (42), as patients may have to take additional medication for their HIV infection (42). Poor adherence to both TB and HIV medication has been found to increase the risk of TB recurrence (41,42). A study conducted by Mutembo et al. (2019), which aimed to estimate the prevalence of recurrent TB among TB cases and compare the risk of unfavourable treatment outcomes between rural and urban settings in the Southern Province of Zambia showed that non-adherence to TB medication was associated with non-adherence to ART, and this was a significant predictor of TB recurrence among HIV-positive patients (41).

1.8.3.7 Duration of TB treatment

The duration of TB treatment is an important factor in preventing TB recurrence (43,44). A study by Menzies et al. (2009) showed that a shorter treatment duration (of six months) increases the risk of TB recurrence, with a 12-month treatment duration associated with a lower risk compared to a 6-month duration (43). In contrast, a study by Mohammed Saif Anaam and Alian A. Alrasheedy (2023), showed that a shorter duration of TB treatment lowers the risk of TB recurrence (44). It was shown in the study that a 6-month treatment duration results in a reduced risk of recurrence (44). Menzies' findings suggest that longer treatment durations may be necessary to prevent TB recurrence. However, longer treatment durations may also have implications for treatment adherence and may also be associated with TB recurrence.

1.8.3.8 Smoking

Smoking is a significant risk factor that has consistently been linked to an increased incidence of tuberculosis recurrence (45,46). In a study by Leung et al. (2015), aimed at investigating treatment outcomes for TB, it was shown that smoking was a risk factor for severe lung disease, lung cavitation, and positive sputum smear and culture at the baseline.

The results of the study suggest that smoking has negative effects on disease severity, treatment outcomes, bacteriological response, and recurrence of TB in patients with TB (45). In another study conducted in Pakistan, by Ahmed et al. (2016), it was shown that smoking was associated with the recurrence of TB among male patients (46). The study also found that smoking was linked to poor adherence to TB medication (46).

1.8.3.9 Multi-drug resistant TB

Studies on TB recurrence have shown a strong correlation between multidrug-resistance TB (MDR-TB) and TB recurrence (9,47,48). In a study conducted by Sun et al. (2017), aimed at evaluating the long-term outcomes of patients who completed TB treatment, with a specific emphasis on multidrug-resistant tuberculosis and TB recurrence (47), it was shown that one-third of the study cohort (29.5%) suffered a recurrence of TB after completing TB treatment, with an overall recurrence rate of 35 per 1000 patient-years (PY), which was significantly higher among MDR-TB patients (65/1000 PY). The study showed that multi-drug resistant TB infection was strongly associated with TB recurrence (47).

1.8.3.10 Weight

Weight has emerged as a significant risk factor for recurrent tuberculosis (TB) in HIV patients on Antiretroviral Therapy (ART), as evidenced by several studies. Malnutrition and lower body weight have been associated with impaired immune responses, making individuals more susceptible to infectious diseases, including TB (49,50). A study conducted by Podewils et al. (2013) reported that malnourished TB patients had a higher risk of TB recurrence after treatment completion (49). Furthermore, a study by Chadha et al. (2020) found that individuals with lower body mass index (BMI) at the time of TB diagnosis were at increased risk of TB recurrence (50).

1.8.4 Conceptual Framework

The risk factors for TB recurrences can be conceptualized as a multifactorial and dynamic interplay of poor treatment adherence, the patient's immunological state, and demographic factors that contribute to the likelihood of experiencing TB recurrence. Figure 1 provides an overview of the components within this framework and outlines the relationship between various factors and the recurrence of TB after treatment.

Possible moderators between patient's immunological state and recurrence of TB are WHO stage of HIV, CD4 count, duration of previous TB treatment, diabetes comorbidity, and hypertension comorbidity. For example, patients who have a low CD4 count may be more likely to experience recurrent TB because their immunity is low than those with a high CD4 count. Patients that are on WHO stage 3, and stage 4 are more likely to experience recurrence of TB than patients at stage 1 and stage 2, because they are at an advanced stage of HIV progression and their immunity may be low. Patients whose duration of previous TB treatment was shorter, may have a high likelihood for recurrent TB than patients who had a longer treatment, because TB may not have been cleared in the patient's body. Patients with diabetes comorbidity can be more prone to recurrent TB than patients who are not diabetic because diabetes is associated with health complications. Literature on hypertension and TB recurrence is scarce, but hypertension may also be a risk factor for TB recurrence, as such, this research will check for the association between hypertension and TB recurrence. Patients with hypertension may have a high likelihood for recurrent TB because hypertension is associated with health complications and can possibly increase the likelihood for recurrent TB among already treated patients. Under patient's demographics, possible moderators can be age and sex. Different age groups may have different chances of experiencing recurrent TB because of occupation exposure. For example, age group between 30 to 39, people tend to work a lot, thereby getting exposed to possible risk for diseases than age groups 60 and above, as most people retire in this age group. Male patients are more likely to experience recurrent TB than female patients because females have better health seeking behaviour than males, as suggested by literature. Possible moderators under treatment related factors can include poor adherence to TB medication and poor adherence to HIV medication. TB Drug resistance would have been a good variable to investigate- however it was not available in the dataset, therefore, for purposes of the study, such linkage would only be idealistic than conclusive.

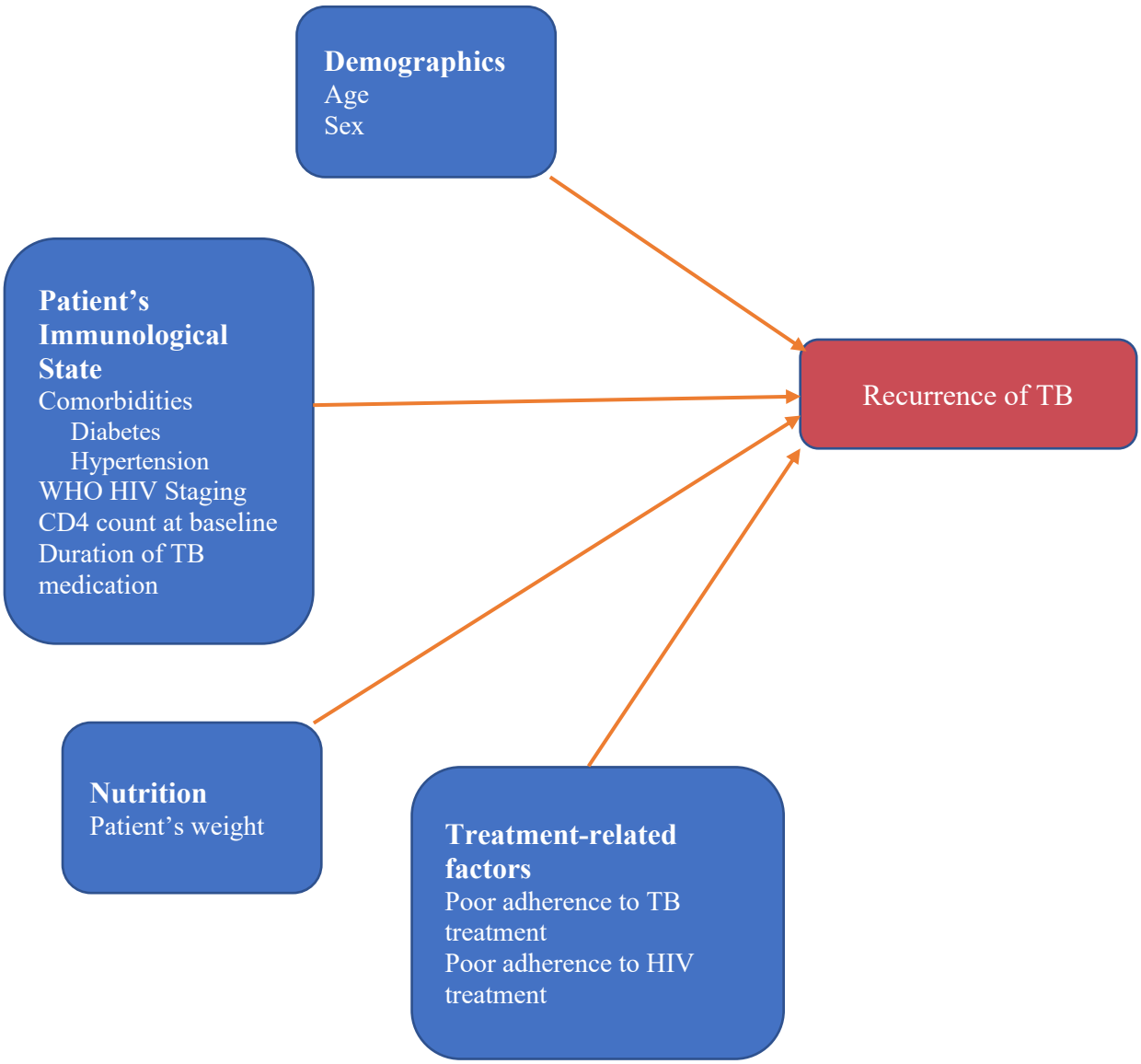

Figure 1.1: Conceptual Framework showing factors associated with TB recurrence

Source: Author's own formulation

CHAPTER 2

2 Methods

This chapter gives information about the study design employed in this research. It also highlights information about the study site, the study population, how the primary data was collected, and how the data was obtained and managed. The statistical methods used, and analysis conducted to address the study objectives are also discussed in this chapter. The chapter concludes with the ethical considerations and limitations of the study.

2.1 Study Site

The study was conducted in MRC/Wits-Rural Public Health and Health Transitions Unit (Agincourt) research area. MRC/Wits-Rural Public Health and Health Transitions Unit (Agincourt) is a health and socio-demographic surveillance system (HDSS) that was established in 1992.

The study area is in rural northeast, South Africa and has South Africa's second-highest HIV prevalence rate (51). The Agincourt HDSS study area comprises 31 villages covering an area of 475 square kilometres with an estimated population of 120,000 people (52). Its population and health priorities resemble many rural communities in Sub-Saharan Africa (52). As such, the MRC/Wits-Agincourt Unit responds to a scope of rural public health issues to produce health research and data which is translatable to other rural Sub-Saharan African communities.

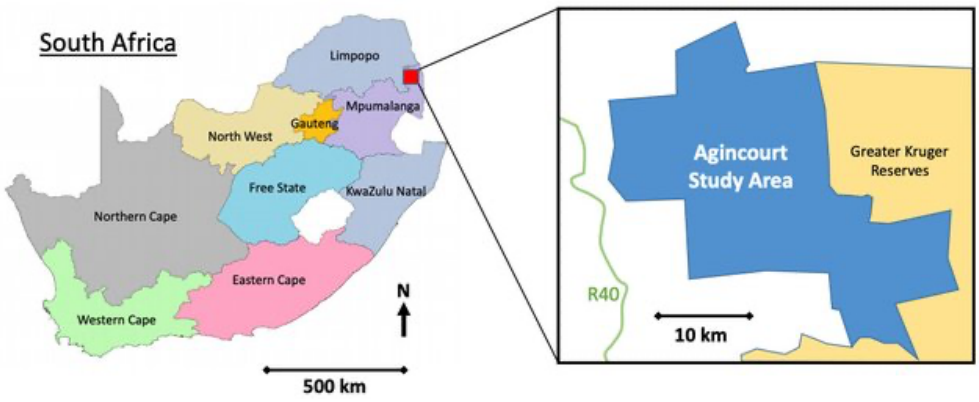

Figure 2.1: Map of research area

2.2 Data Source and Description of the Primary Study

This study used data from the Agincourt Health and Demographic Surveillance System (HDSS) clinic link study. The data is collected by trained field workers. “Every HIV patient has a clinical file that is created upon first registration at an ART clinic and is updated at each clinic visit. Following the clinic visit, visit-level information from the patient file is entered into an electronic database” (53). The data consists of patients’ demographics (age and sex), clinical data (WHO stage of HIV, duration of TB medication), and other conditions (diabetes and hypertension), collected from patients visiting nine public health facilities within the study area.

The record of each patient enables the monitoring and evaluation of their HIV treatment and overall health status. By capturing important details such as age, sex, and clinical data including the WHO stage of HIV and duration of TB medication, the data provides valuable insights into the patient's progress and response to treatment. Additionally, the inclusion of other conditions like diabetes and hypertension allows for a comprehensive understanding of the patient's overall health profile. Moreover, the electronic database ensures the accessibility and integrity of the data, promoting efficient data analysis and the generation of evidence-based interventions and strategies to enhance the quality of care provided to HIV patients in the study area.

2.3 Study Design

This was a retrospective cohort study investigating risk factors for the recurrence of TB among HIV patients who are on anti-retroviral treatment in rural northeast, South Africa, between 1st January, 2014 and 31st December, 2022.

2.4 Inclusion and Exclusion Criteria

HIV patients on ART who received a TB diagnosis (pulmonary TB or extrapulmonary TB) at least once during the study period (1st January, 2014 – 31st December, 2022) and were at least 18 years old made up the study population. The study included all HIV patients on ART that were diagnosed and treated for TB at any time within the study period (1st January, 2014 – 31st December, 2022). Thus, enrolment was staggered. All patients that were less than 18 years old, were excluded from the study.

2.5 Study Population

There were 24,481 participants that were diagnosed and treated for HIV during the study duration (1st January, 2014 to 31st December, 2022). 100 participants were excluded because their information was missing from another dataset ("individuals" – containing participants' demographic information), leaving 24,381 participants. 823 patients were removed because they were less than 18 years old, and 23,558 remained. From this population, 8,384 participants were diagnosed and treated for TB at least once during the study period. From this population three were excluded because they were not in the other dataset (diagnoses dataset). 1,828 participants were removed because they had missing dates, 3 were excluded because their enrolment date did not meet the inclusion criteria (they enrolled before 2014), 626 patients were removed because they were from clinics where data collection was stopped (Thulamahashe, Rolle and Cork) before the last day of follow up (31st December, 2022). Upon setting the data to survival data, 1,126 patients were removed because their last visit dates (end of their first TB episode) were the same as the dates for the beginning of the follow up dates. After excluding those who did not meet the inclusion criteria, and removing those with missing data, 4,803 were eligible for enrolment into the study.

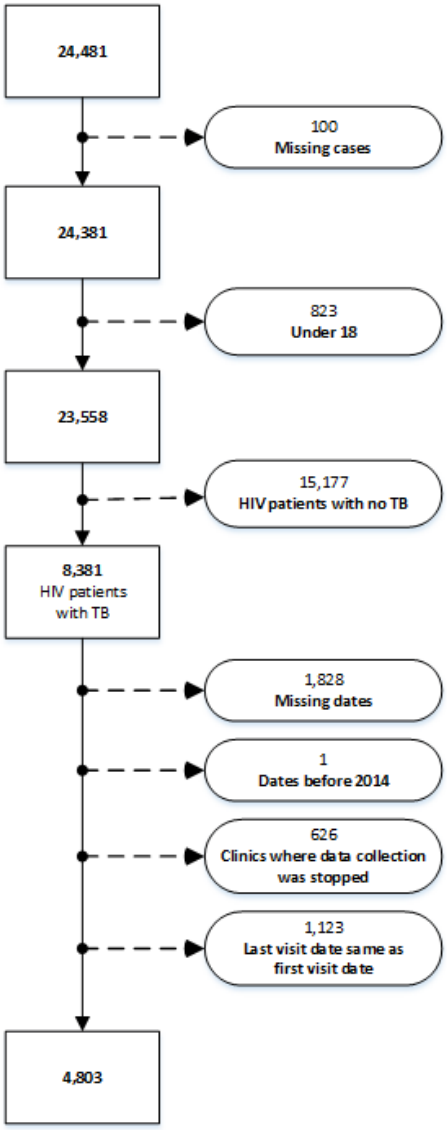

Figure 2.2: Flow Chart showing how participants were selected for analysis

2.6 Power Calculation

Power calculation was done in Stata to estimate the required sample size and ensure adequate statistical power in the study. According to the first national TB survey in South Africa (2018), the expected proportion of individuals who will experience a recurrence of TB is 14% males and 10% females (13). Using estimates from the TB survey in South Africa, a power of 0.97 was detected (refer to appendix B for the Stata output).

Thus, with a population of 4,803, the study's estimated power to identify a distinction between the expected proportion of individuals experiencing TB recurrence and the null hypothesis proportion in two groups was 0.97 or 97%.

2.7 Data Management

STATA 17 SE was used for data cleaning, management as well as analysis. Before statistical analysis was done, duplicates were checked for, no duplicates were found. The data did not contain any personal identifiers prior to use. The data was coded, recoded and variables labelled appropriately as presented in Table 2.1.

2.7.1 Outcome variable: recurrent TB

This is a dichotomous variable derived from investigating if a participant experienced another episode of TB one year after being treated for TB. Another episode of TB one year or after one year of treatment to denote recurrent TB. The category "recurrent TB" was codes as "1" and "no recurrent TB" coded as "0".

2.7.2 Explanatory variables

The explanatory variables explored in this study were participants' age, sex, weight, diabetes comorbidity, hypertension comorbidity, WHO stage of HIV, CD4 count at baseline, duration of previous TB treatment, poor adherence to TB treatment, and poor adherence to HIV treatment. Table 2.1 shows how these variables were operationalised in this study.

Age was measured in years, and it was categorized into five age groups: 18-29, 30-39, 40-49, 50-59, and 60 and above. Each participant was assigned to one of these age groups based on their age at the time of the first TB episode. Sex was recorded as either male or female, with

the following coding: Male=1 and Female=2. Weight was measured in kilograms. In the regression analysis, the weight variable was treated as a unit of five kilograms.

“Diabetes comorbidity” and “hypertension comorbidity” were combined into a single variable called “Comorbidities” and were coded as follows: No comorbidities (no diabetes and no hypertension) = 0, and comorbidities (either diabetes or hypertension), and two comorbidities (both diabetes and hypertension) = 1. This is because, they were only four participants with diabetes, and only two participants with both diabetes and hypertension.

"WHO Stage (HIV)" represents the HIV stage of each participant. It was categorised into four categories (1, 2, 3, and 4) based on the standard WHO staging of HIV progression. The variable was coded as follows: Stage 1=1, Stage 2=2, Stage 3=3, and Stage 4=4. Baseline CD4 count was measured in cells/mm^3, and in the regression analysis, it was treated as a unit of 10 cells/mm^3. The duration of previous TB treatment was measured in weeks. In the regression analysis, it was converted into months.

Poor TB Treatment Adherence: This variable indicates whether a participant showed poor adherence to TB treatment, and it was coded as follows: No poor TB treatment adherence (indicating good adherence) =0, and Poor TB treatment adherence (indicating poor adherence) =1. Poor HIV Treatment Adherence: Like poor TB treatment adherence, this variable indicates whether a participant showed poor adherence to HIV treatment. It was coded as follows: No poor HIV treatment adherence (indicating good adherence) =0, and Poor HIV treatment adherence (indicating poor adherence) =1.

Table 2.1: Variables of Interest in the study

VARIABLES OF INTEREST		
Outcome Variable		
Variables	**Definition**	**Application**
Recurrent TB	Another episode of TB after one year of treatment of the first episode.	Those that had another TB diagnosis and were taking TB medication after one year of treatment of the first episode (recurrent TB) were coded as "1", and those with no other episode by the end of the study or those that left the study during the study period (censored) were coded as "0". The study will consider only the first recurrence.
Recurrence time	The recurrence time was defined as the duration after the treatment of the first episode to the occurrence of another TB episode (TB recurrence).	It was applied as a numerical value, with a median of 1.93 yeas and a range of 1 to 8.66 years.
Explanatory Variables		
Variables	**Definition**	**Application**
Age	Age in years from birth to the first episode of TB	This is a continuous variable measured in years. It was categorized as: 1=18 – 29 2=30 – 39 3=40 – 49 4=50 – 59 5= 60+
Sex	Participant's gender, categorized as Male or Female.	This is a categorical variable with two categories – male and female, coded as follows: 1=Male 2=Female
Weight	Weight in kilograms at the time of the first episode.	This is a continuous variable measured in kilograms. In the regression analysis a unit of five kilograms was used.
Comorbidities	If the participant was diagnosed with diabetes and or hypertension and was receiving treatment for diabetes and or hypertension at the time they had the first episode of TB.	In this study, this variable was categorized and coded as follows: 0=No comorbidities 1= Comorbidities

Variables	Definition	Application
WHO stage (HIV)	Refers to a classification system developed by the World Health Organization (WHO) to assess the progression and severity of HIV infection in individuals. It categorizes HIV infection into four stages (1, 2, 3, 4) based on the clinical manifestations and immune status of the affected person.	In this research, this is a categorical variable, coded as follows: 1=Stage 1 (Asymptomatic HIV) 2=Stage 2 (Mild Symptomatic HIV) 3=Stage 3 (Advanced Symptomatic HIV) 4=Stage 4 (Severe HIV [AIDS])
Baseline CD4 Count	CD4 count (measured in cell/mm^3) of the patient at the time they first were diagnosed and treated for TB.	This was a continuous variable measured in cells/mm^3. In the regression analysis, a unit of 10 cells/mm^3 was used.
Duration of previous TB treatment	Refers to the length of time that an individual who was diagnosed with the first TB episode has been on TB treatment.	In this study, this is a continuous variable, measured in weeks. In the regression analysis it was measured in months.
Poor TB treatment adherence	Refers to a situation where a patient with tuberculosis does not follow the recommended treatment plan as prescribed by their healthcare provider. This can include missing doses of medication, interrupting treatment before the recommended duration, or not completing the full course of treatment. In this study, "poor tuberculosis treatment adherence" means missing clinic appointment for drug refill for 60 days or more than 60 days (2,3).	In this study, this is a categorical variable, coded as follows: 0=No poor TB treatment adherence 1=poor treatment adherence
Poor HIV treatment adherence	Refers to a situation where a patient with HIV does not follow the recommended treatment plan as prescribed by their healthcare provider. This can include missing doses of medication, interrupting treatment before the recommended duration, or not completing the full course of treatment. In this study, "poor HIV treatment adherence" means missing clinic appointment for drug refill for 60 days or more than 60 days (2,3).	In this study, this is a categorical variable, coded as follows: 0=No poor HIV treatment adherence 1=Poor HIV treatment adherence

2.8 Statistical analysis

Descriptive statistics were carried out on all variables. For categorical variables, frequency distribution tables were used, and frequency and percentage for each variable were calculated and presented. Tests for normality were conducted on continuous variables which included participants' weight, CD4 count at baseline, and duration of previous TB treatment, and the data was found not normally distributed (see appendices C, D and E), so for those variables, median, interquartile range (IQR) and range were calculated and presented.

Objective 1: To determine the incidence rate of TB recurrence after successful treatment among HIV patients who are on ART in rural northeast, South Africa

Incidence rate was calculated in Stata, using the "strate" command, and was set at "per 100" – thus per 100 years.

Objective 2: To determine the time to another TB episode after successful TB treatment in HIV patients who are on ART in rural northeast, South Africa

To determine the time to another episode of TB from successful TB treatment, the Kaplan-Meier curves were used to visualize and compare group-specific recurrence probabilities of TB over time.

Objective 3: To identify risk factors for TB recurrence after successful treatment among HIV patients who are on ART in rural northeast, South Africa

The Cox regression model was fitted to investigate factors associated with the recurrence of TB in individuals over time, after successful treatment. The fitness of the cox regression model was investigated using the Cox-Snell residual plot (see appendix F in the appendices).

2.9 Study Limitations

A notable limitation of this study lies in the restricted scope of variables as this was secondary data analysis. If the scope of variables was expanded, it could have unveiled a more holistic comprehension of the factors associated with recurrent TB among HIV patients who are on ART in the rural northeast, South Africa. The absence of data on viral load, line of treatment for ART, height of the patients (to measure BMI), socioeconomic status, smoking habits, and alcohol consumption of the participants represents a limitation for a more comprehensive and in-depth analysis. These additional variables hold immense potential to enrich the findings, offering valuable insights into the interplay between various socio-behavioural and health-related factors influencing TB recurrence.

2.10 Ethical Consideration

Ethical clearance for this study was obtained from the Human Research Ethics Committee (Medical) of the University of Witwatersrand, clearance certificate number: M230409 MED23-02-201. (See copy in the appendices – Appendix G). And permission to use data was granted by MRC/Wits-Rural Public Health and Health Transitions Unit (see copy in the appendices – Appendix H).

CHAPTER 3

3 Results

The data analysis performed using the methods described in Chapter 2 is presented in this chapter along with the findings. Frequency tables were used to compile the descriptive statistics for the population, and the results are presented in tables in chronological sequence based on the study's goals. The table that follows in this chapter's conclusion presents the hazard ratios and 95% confidence intervals from the univariable and multivariable Cox regression analysis, which looks at the factors that increase the likelihood for TB recurrence over time.

3.1 Sample Characteristics

In this research, a follow-up was conducted on 4,803 HIV patients receiving Antiretroviral Therapy (ART) from the rural northeast, South Africa, who had previously been diagnosed and treated for tuberculosis between January 1, 2014, and December 31, 2022. Out of the 4,803 patients, 396 experienced the outcome of interest (recurrent TB), and 4,407 were censored because they never experience the event during the study duration. The study participants' characteristics, including demographic and clinical data, are presented in Table 1.

Among the study participants, 27.6% (1,326) were male, while 72.4% (3,477) were female. The patients' weight ranged from 29 kgs to 165 kgs, with a median weight of 66 kgs and an interquartile range of 58.0 – 77.0 kgs. Regarding age distribution, 24.8% (1,189) of the patients were between 18 to 29 years old, 34.5% (1,657) were aged between 30 to 39 years, 23.1% (1,110) fell in the 40 to 49 years age group, 11.0% (527) were between 50 to 59 years old, and 6.6% (319) were 60 years old and above. In terms of WHO HIV staging, the majority (84.7%, 3,188) were on stage one, while 7.6% (286) were on stage two, 7.0% (263) on stage three, and only 0.7% (28) on stage four.

Additionally, 18.3% (881) had no comorbidities, while 81.7% (3,922) had comorbidities. The adherence rates to both TB and HIV medications were relatively high, with 91.4% (4,391) adherent to TB medication and 88.0% (4,228) adherent to HIV medication.

Out of the total participants, (8.2%) 396 experienced recurrent TB, while (91.8%) 4,407 did not. Among those with recurrent TB, 36.1% (143) were male, and 63.9% (253) were female. On the other hand, out of those without TB recurrence, 26.8% (1,183) were male, and 73.2% (3,224) were female. The median weight for recurrent TB cases was 63.0 kgs, with an interquartile range of 54.2 – 70.0 kgs. In contrast, those without TB recurrence had a median weight of 66.5 kgs, with an interquartile range of 58.0 – 77.3 kgs.

Regarding age distribution among recurrent TB cases, 24.5% (97) were between 18 to 29 years old, 37.1% (147) were between 30 to 39 years old, 24.0% (95) were between 40 to 49 years old, 9.1% (36) were between 50 to 59 years old, and 5.3% (21) were 60 years old and above. Among those without TB recurrence, 24.8% (1,092) were between 18 to 29 years old, 34.3% (1,510) were between 30 to 39 years old, 23.0% (1,015) were between 40 to 49 years old, 11.1% (491) were between 50 to 59 years old, and 6.8% (298) were 60 years old and above.

Furthermore, 67.1% (204) of the recurrent TB cases were on stage one of the WHO HIV staging, 9.2% (28) on stage two, 21.7% (66) on stage three, and 2.0% (6) on stage four. In comparison, among those without TB recurrence, 86.2% (2,984) were on stage one, 7.5% (258) on stage two, 5.7% (197) on stage three, and 0.6% (22) on stage four.

Among the recurrent TB cases, 18.2% (72) had comorbidities, and 81.8% (324) had no comorbidities. On the other hand, among those without recurrent TB, 18.4% (809) had comorbidities, and 81.6% (3,598) had no comorbidities.

Regarding medication adherence, 6.3% (25) of the recurrent TB patients were not adherent to their TB medication during their first TB episode, and 10.4% (41) were not adherent to their HIV medication. Among those without TB recurrence, 8.8% (387) were not adherent to their TB medication during their first TB episode, and 12.2% (534) were not adherent to their HIV medication.

Table 3.1: Characteristics of the study population for recurrent TB among HIV patients on ART

Variables	Totals	Recurrent TB (N, %)	No Recurrent TB (N, %)
	4,803 (100)	396 (8.2)	4,407 (91.8)
Sex			
Male	1,326 (27.6)	143 (36.1)	1,183 (26.8)
Female	3,477 (72.4)	253 (63.9)	3,224 (73.2)
Weight (Kgs)	(N=3,663)	(N=305)	(N=3,358)
Median, (IQR), (Range)	66, (58 – 77), (29 – 165)	63, (54.2 – 70), (34 – 160)	66.5, (58 – 77.3), (29 – 165)
Participant's Age (years)			
18 – 29	1,189 (24.8)	97 (24.5)	1,092 (24.8)
30 – 39	1,657 (34.5)	147 (37.1)	1,510 (34.3)
40 – 49	1,110 (23.1)	95 (24.0)	1,015 (23.0)
50 – 59	527 (11.0)	36 (9.1)	491 (11.1)
60+	319 (6.6)	21 (5.3)	298 (6.8)
WHO stage (HIV)			
Stage 1	3,188 (84.7)	204 (67.1)	2,984 (86.2)
Stage 2	286 (7.6)	28 (9.2)	258 (7.5)
Stage 3	263 (7.0)	66 (21.7)	197 (5.7)
Stage 4	28 (0.7)	6 (2.0)	22 (0.6)
CD4 Count (Cells/mm^3)	(N=4,595)	(N=386)	(N=4,209)
Median, (IQR)	229, (112 – 390)	184.5, (76 – 321)	235, (117 – 395)
Duration of previous TB treatment (Weeks)			
Median, (IQR)	31, (16 – 49)	21, (12 – 35)	32, (17 – 50)
Comorbidities			
Comorbidities	881 (18.3)	72 (18.2)	809 (18.4)
No comorbidities	3,922 (81.7)	324 (81.8)	3,598 (81.6)
Poor Adherence to TB medication			
Yes	412 (8.6)	25 (6.3)	387 (8.8)
No	4,391 (91.4)	371 (93.7)	4,020 (91.2)
Poor Adherence to HIV medication			
Yes	575 (12.0)	41 (10.4)	534 (12.1)
No	4,228 (88.0)	355 (89.6)	3,873 (87.9)

3.2 Incidence rate of recurrent TB among HIV patients who are on ART in rural northeast

Table 2 presents the incidence rates of recurrent tuberculosis among HIV patients receiving ART in the rural northeast, South Africa during the period from January 1, 2014, to December 31, 2022, stratified by various demographic and clinical characteristics.

The number of HIV patients on ART followed up in this study was 4,803, and 396 recurrent cases were observed during the study period. The recurrence rate was 3.0 per 100 person years (py), (95% CI: 2.7 – 3.3). The total time at risk was 13,142.40 person years.

There was a statistically significant difference in the recurrence rate of HIV patients on ART by the patient's sex, WHO stage of HIV, and their adherence to TB medication during the previous episode of TB. Age of the patient, comorbidities, and poor adherence to HIV medication by the patient (during the previous episode of TB) were not statistically significant on the log-rank test.

The recurrence rate was higher in men than women, with that of men at 4.3 per 100 person years, and that of women at 2.6 per 100 person years. The recurrence rate was slightly higher in among the people of ages between 40 – 49 years old, at 3.3 per 100 person years, followed by people aged between 30 – 39 years old, at 3.2 per 100 person years. Then among those aged between 18 – 29 years old, the recurrence rate was 2.8 per 100 person years, and among people aged between 50 – 59 years old, and those at 60 years old and above, the recurrence rate was 2.6 per 100 person years.

Patients who were on stage 4 and stage 4 of the WHO HIV staging had a higher recurrence rate, at 8.7 per 100 person years and 8.4 per 100 person years respectively, while the recurrence rate among those at stage 2 and stage 1 was at 3.1 per 100 person years and 2.4 per 100 person years respectively.

The recurrence rate was higher in patients who had no comorbidities as compared to those with comorbidities; 3.1 per 100 person years vs 2.6 per 100 person years. Patients that were not adherent to their TB medication had a higher recurrence rate, at 3.8 per 100 person years than those that were adherent to their TB medication, whose recurrence rate was at 2.8 per 100 person years. Among those that were not adherent to their HIV medication, the recurrence rate was at 3.3 per 100 person years, slightly higher than that of those who were adherent to their HIV medication, which was at 3.0 per 100 person years.

Table 3.2: Tuberculosis recurrent rates by various variables

Factor	Categories	Number	Recurrent cases	Follow-up (10^2 py)	Recurrence rate (10^2 py) (95% CI)	Logrank P-val
Overall		4,803	396	131.4	3.0 (2.7 – 3.3)	
Sex	Male	1,326	143	33.6	4.3 (3.6 – 5.0)	
	Female	3,477	253	97.8	2.6 (2.3 – 2.9)	<0.001
Age						
	18 – 29	1,189	97	34.3	2.8 (2.3 – 3.4)	
	30 – 39	1,657	147	46.1	3.2 (2.7 – 3.8)	
	40 – 49	1,110	95	29.1	3.3 (2.7 – 4.0)	0.55
	50 – 59	527	36	14.0	2.6 (1.9 – 3.6)	
	60+	319	21	8.0	2.6 (1.7 – 4.0)	
WHO Stage (HIV)						
	Stage 1	3,188	204	83.8	2.4 (2.1 – 2.8)	
	Stage 2	286	28	9.1	3.1 (2.1 – 4.5)	
	Stage 3	263	66	7.9	8.4 (6.6 – 10.7)	<0.001
	Stage 4	28	6	0.7	8.7 (3.9 – 19.4)	
Comorbidities						
	Comorbidities	881	72	27.4	2.6 (2.1 – 3.3)	
	No comorbidities	3,922	324	104.1	3.1 (2.8 – 3.5)	0.09
Poor Adherence to TB medication	Yes	4,391	25	6.6	2.6 (2.1 – 3.3)	
	No	412	371	124.8	3.1 (2.8 – 3.5)	0.02
Poor Adherence to HIV medication	Yes	4,228	41	12.3	3.3 (2.5 – 4.5)	
	No	575	355	119.1	3.0 (2.7 – 3.3)	0.17

3.3 Time to another TB episode after successful treatment

In this study, time to subsequent TB episodes for each recurrent TB case was calculated. The minimum time to another TB episode was 0.02 years (7 days), indicating that some individuals experienced TB recurrence just a week after their initial episode. The median time to another TB episode was found to be 1.93 years, signifying that approximately 50% of subjects experienced TB recurrence within this duration. The maximum time to another TB episode was 8.66 years, suggesting that in some cases, the interval between recurrent TB episode and the first episode could extend to up to eight years.

The time to TB recurrence was modelled using Kaplan Meier survival plots disaggregated by the various variables. The Log-rank test is used to establish the significance of variations in TB recurrence between various groups as indicated by the variable used for stratification at a confidence level of 95%. The following Kaplan Meier curves estimate the survival function of TB recurrence over time.

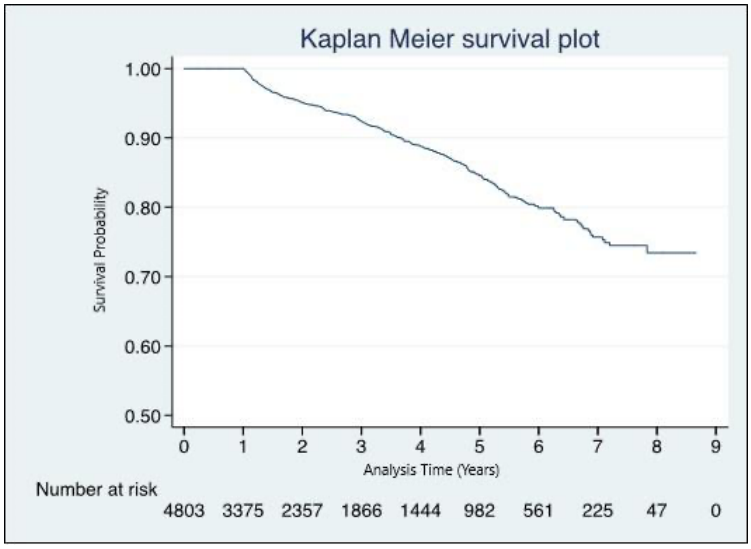

Figure 3.1: Risk of TB recurrence over time

Figure 3.1 exhibits diminishing cumulative survival probabilities for TB recurrence over time. This indicates over the years; it is more likely that TB will recur. However, it is about 75% more likely that a patient will not have a recurrence of TB after year 7.

The Kaplan Meier plot in Figure 3.2 shows the risk of TB recurrence stratified by sex. The curve for males falls faster over the years for males than for the curve for females.

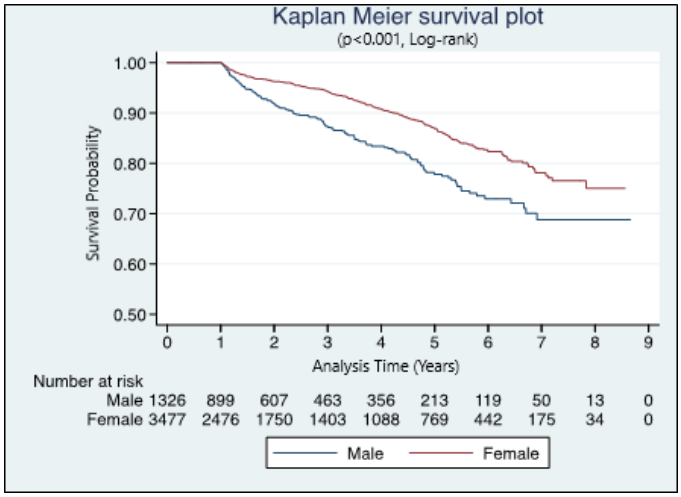

Figure 3.2: Risk of TB recurrence over time, stratified by sex

This indicates that the probability of survival diminishes at a relatively higher rate for males than females over the years. This translates to a relatively higher chance of TB recurrence for males than for females over time. The Log-rank p-value (0.001) shows that this discrepancy in survival rates between the sexes is statistically significant.

In Figure 3.3, the Kaplan Meier plot further stratifies the risk of TB recurrence by WHO HIV staging. While the curve for HIV stage 1 patients falls absolutely at the lowest rate followed by HIV stage 2 patients, HIV stage 3 and HIV stage 4 patients' curves overlap over time.

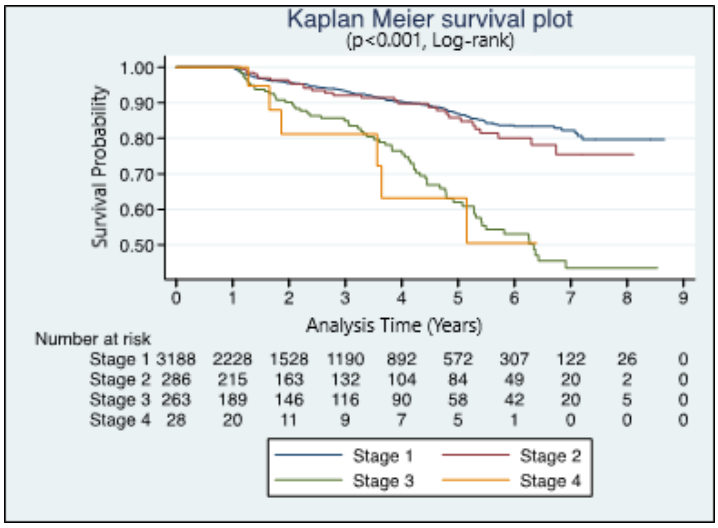

Figure 3.3: Risk of TB recurrence over time, stratified by WHO stages of HIV

This observation in Figure 3.3 indicates that the chance of TB recurrence is lowest for stage 1 patients followed by stage 2 patients whereas the risk of TB recurrence in stage 3 and stage 4 patients shifts substantially over time. The Log-rank p-value (<0.001) in this stratification also suggests that the observed variation in survival rates across patients in the 4 HIV WHO stages is statistically significant.

The risk of TB recurrence stratified by comorbidities is hereinafter depicted by the Kaplan Meier curve in Figure 3.4

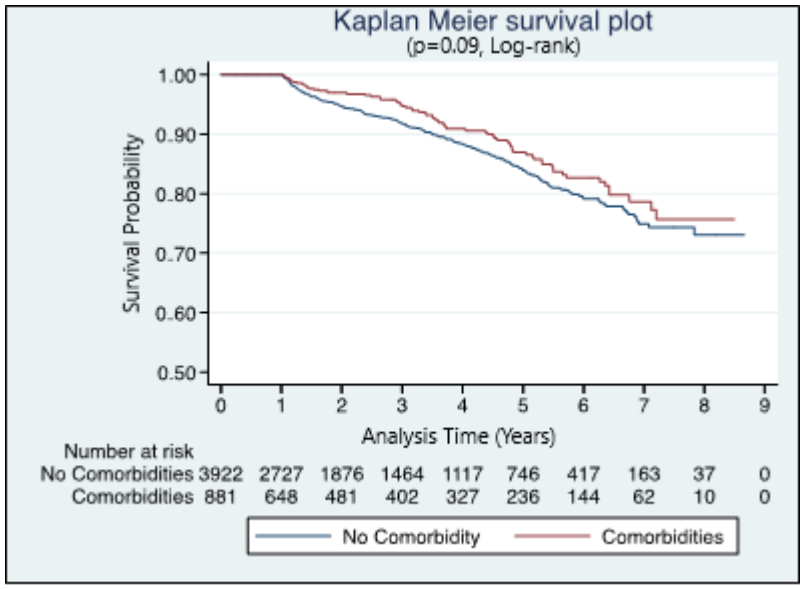

Figure 3.4: Risk of TB recurrence over time, stratified by comorbidities

The curve of patients with no comorbidities falls faster over the years than the curve for patients with comorbidities. This is indicative that it is more likely for patients with no comorbidities to experience a recurrence of TB over time than patients with comorbidities. However, it is evident that this observation confers to events that occur by chance as the Log-rank test (p=0.09) suggests that this observation is statistically insignificant.

The risk of TB recurrence is also stratified by patients' adherence to medication for TB and HIV respectively in Figure 3.5 and Figure 3.6.

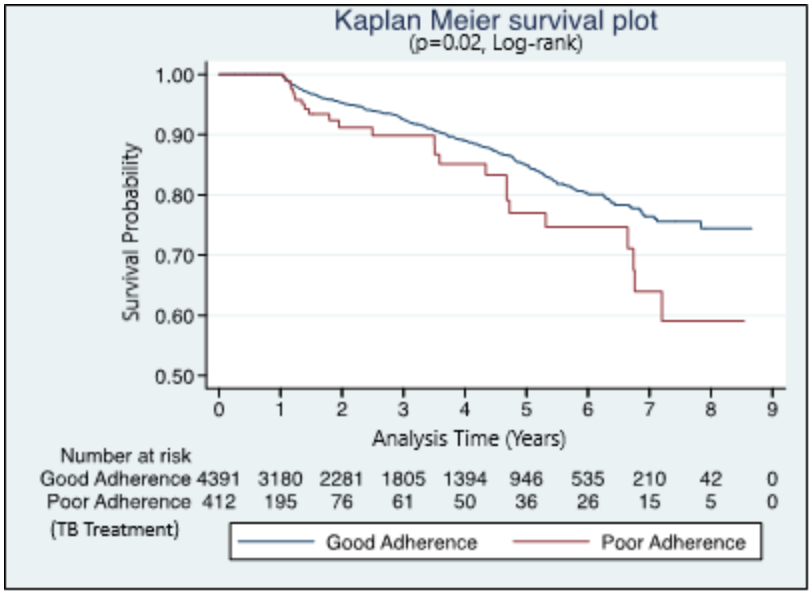

Figure 3.5: Risk of TB recurrence over time, stratified by TB treatment adherence

The Kaplan Meier curve in Figure 3.5 has the curve for patients with poor adherence to TB treatment falling faster than the curve for patients with good adherence to TB treatment. Intuitively, this observation indicates that the likelihood of TB recurring is higher over the years for patients with poor adherence to TB treatment than those that have good adherence to TB treatment. With a log-rank p-value of 0.02, this observation is statistically insignificant.

Similarly, the Kaplan Meier plot in Figure 3.6 has the curve for good adherence to HIV medication falling relatively slower than the curve for patients with poor adherence to HIV medication.

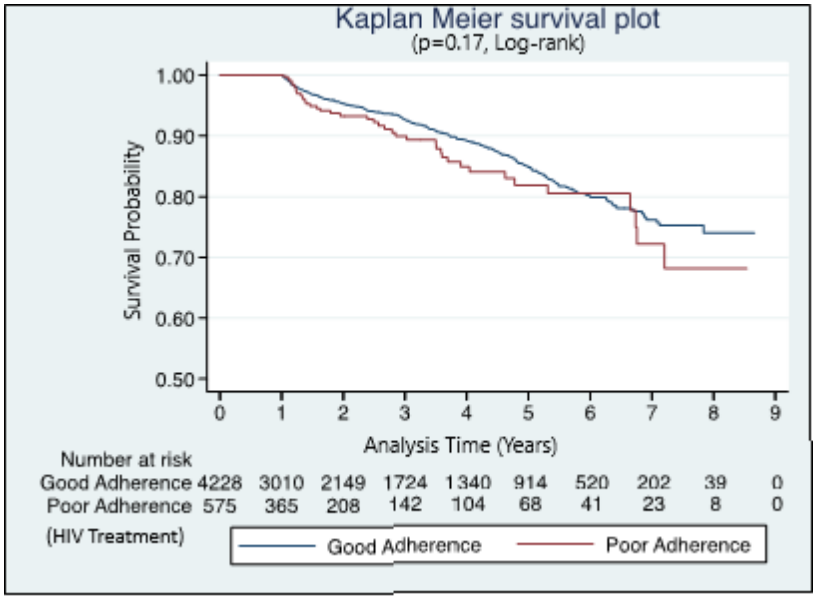

Figure 3.6: Risk of TB recurrence over time, stratified by HIV treatment adherence

This likewise shows that patients with poor adherence to HIV medication are more likely to suffer a recurrence of TB than patients with good adherence to HIV medication. However, an overlapping risk is observed after 6 years where it momentarily becomes less likely for poor medication adherence patients to experience a recurrence in TB than those who adhere well to HIV medication. However, this variation in survival rates by adherence to HIV treatment is statistically insignificant as indicated by the Log-rank test (p=0,17).

3.4 Risk factors for recurrent TB among HIV patients who are on ART in rural northeast

Table 3.3 shows the results of the risk factors for recurrent TB among HIV patients in rural northeast, South Africa.

In the univariable Cox proportional hazards regression analysis, the patient's sex, weight, WHO stage of HIV, CD4 count at baseline, duration of previous TB treatment, and poor adherence to TB medication were found to be significant predictors of recurrence of TB.

Male patients were 73% more likely to experience recurrent TB than female patients (HR=1.73, 95% CI: 1.41 – 2.12). Patients with increased weight were less likely to experience recurrent TB. In univariable analysis, it was found that for each five kilograms increase in weight of the patient, there was 9% decrease in the risk of recurrent TB (HR=0.91, 95% CI: 0.87 – 0.95).

Patients who were at stage three of the WHO HIV stages, were 3.29 times more likely to experience recurrent TB compared to those at stage one (HR=3.29, 95% CI: 2.49 – 4.34). Patients at stage four were 3.62 times more likely to experience recurrent TB as compared to those at stage one (HR=3.62, 95% CI: 1.61 – 8.16). Patients with a low CD4 count at baseline had a high likelihood for experiencing recurrent TB than those with a high CD4 count at baseline. For every 10 cells/mm^3 increase in CD4 count at baseline, the hazard of recurrent TB decreased by 0.98 (HR=0.98, 95% CI: 0.98 – 0.99).

Patients with a longer duration of TB treatment were at a higher risk of recurrence of TB as compared to those with a short duration of TB treatment. In this research, it was found that, for every one month increase in the duration of TB treatment, the risk of recurrent TB increased by a factor of 0.96 (HR=0.96, 95% CI: 0.93 – 0.98). Patients who were not adherent to their TB medication were more likely to experience recurrent TB than those who were adherent to their TB medication. Those that were not adherent were 60% more likely to experience recurrent TB (HR=1.60, 95% CI: 1.07 – 2.40).

The factors: patient's age, comorbidities, and poor adherence to HIV medication were found not to be associated with the recurrence of TB among HIV patients who are on ART in rural northeast, South Africa.

In the multivariable analysis, after adjusting for all other variables in the model, it was found that the factors that were associated with recurrence of TB among HIV patients on ART in the rural northeast, South Africa were: sex of the patient, WHO stage (HIV) of the patient, baseline CD4 count of the patient, and duration of previous TB treatment of the patient.

Male patients were 48% more likely to experience recurrent TB as compared to female patients (HR=1.48, 95% CI: 1.12 – 1.96), while adjusting for other variables. Patients at stage three of the WHO stages of HIV staging were 2.53 time more likely to experience recurrent TB as compared to patients at stage two (AHR=2.53, 95% CI: 1.81 – 3.54), while adjusting for other variables. Patients with a low CD4 count at baseline were more likely to experience recurrent TB than patients with high CD4 count at baseline. For every 10 cells/mm^3 increase in CD4 count at baseline, there was a 1% decrease in the likelihood for TB recurrence (AHR=0.99, 95% CI: 0.98 – 0.99).

Patients who had a longer duration of TB treatment were found to be more likely to experience recurrent TB as compared to patients with a short duration of TB treatment. For each one month increase in the duration of TB treatment, the hazard of recurrent TB was 0.95 (AHR=0.95, 95% CI: 0.92 – 0.98), while adjusting for other variables.

Patient's age, weight, comorbidities, poor adherence to TB medication, and poor adherence to HIV medication were found to be not statistically significant factors associated with recurrence of TB, in the multivariate analysis.

Table 3.3: Risk factors associated with recurrent tuberculosis

Variables	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Sex				
Female	ref	-		
Male	1.73 (1.41 – 2.12)	<0.001	1.48 (1.12 – 1.96)	0.007
Weight (5kgs)	0.91 (0.87 – 0.95)	<0.001	0.97 (0.92 – 1.02)	0.22
Age				
18 – 29	ref	-		
30 – 39	1.14 (0.88 – 1.47)	0.33	0.80 (0.58 – 1.10)	0.17
40 – 49	1.19 (0.90 – 1.59)	0.22	0.83 (0.57 – 1.23)	0.36
50 – 59	0.93 (0.63 – 1.36)	0.70	0.72 (0.42 – 1.24)	0.24
60+	0.96 (0.60 – 1.53)	0.85	1.01 (0.54 – 1.88)	0.97
WHO stage (HIV)				
Stage 1	ref			
Stage 2	1.17 (0.79 – 1.73)	0.45	1.09 (0.71 – 1.68)	0.68
Stage 3	3.29 (2.49 – 4.34)	<0.001	2.53 (1.81 – 3.54)	<0.001
Stage 4	3.62 (1.61 – 8.16)	<0.002	0.68 (0.09 – 4.98)	0.71
CD4 Count (10 Cells/mm^3)	0.98 (0.98 – 0.99)	<0.001	0.99 (0.98 – 0.99)	<0.001
Duration of previous TB treatment (months)	0.96 (0.93 – 0.98)	<0.001	0.95 (0.92 – 0.98)	0.001
Comorbidities				
No comorbidities	ref	-		
Comorbidities	0.80 (0.62 – 1.03)	0.09	0.73 (0.49 – 1.09)	0.13
Poor Adherence to TB medication				
No	ref			
Yes	1.60 (1.07 – 2.40)	0.02	1.40 (0.76 – 2.60)	0.29
Poor Adherence to HIV medication				
No	ref	-		
Yes	1.25 (0.91 – 1.73)	0.17	1.38 (0.85 – 2.24)	0.19

CHAPTER 4

4 Discussion

This study determined the incidence of recurrent TB among HIV patients who are on ART in rural northeast, South Africa. The study also determined the time to another TB episode after successful treatment and identified the risk factors for recurrent TB in the same population. This chapter discusses this study's key findings based on each objective, and how they relate to existing knowledge. The chapter concludes with the strengths and limitations of the study.

4.1 The incidence rate of recurrent TB among HIV patients on ART

This study found that the incidence of recurrent TB in the study population is 3.0 per 100 person years. This finding aligns with previous research conducted in Malawi, a similar geographical region, where it was reported that HIV-infected individuals had an incidence rate of recurrent TB at 2.2 per 100 person-years (23). Similarly, a systematic review of TB recurrence rates in HIV-positive individuals on ART in sub-Saharan Africa found rates ranging from 1.7 to 2.8 per 100 person-years (54). Another systematic review and meta-analysis of the incidence rates, proportions of relapse and reinfections of studies published in English, French, and Spanish between January 1, 1980, and September 30, 2020 found a pooled incidence rate of recurrent TB after successful treatment of 2.26 per 100 person-years (95% CI 1.87 – 2.73) (7). Contrary to the findings in this study, a study in Cape Town, South Africa that was conducted to investigate the recurrence rate of TB in patients after treatment, found that the recurrence rate was 16.4 per 1000 person-years (5). The study reported a higher incidence rate than this study. The difference may be because of the differences in the study settings.

In this study, the recurrence rate was found to be higher in males compared to females, which aligns with some previous research on TB recurrences. In a study by Mahmood et. al. (2015), a higher incidence rate among males was reported, with the recurrence rate at 8.7% in men, and 7.9% in women (27). This gender difference may be attributed to various factors, including differences in healthcare-seeking behaviour, as females have better health seeking behaviour than males (34).

In this study, the recurrence rate was found to be higher among patients who were on WHO stage three, and stage four as compared to those on stage one and stage two. Similar findings were reported in a study conducted by Stephen et. al. on tuberculosis among HIV-infected patients receiving HAART, which aimed to determine long-term incidence and risk factors in a South African cohort. The study found a higher incidence among patients with WHO HIV stage 3 or 4 disease (5.71 and 3.88/100 person-years, respectively) (35). This indicates that the severity of the disease, as classified by the WHO HIV stages, is associated with an increased risk of TB recurrence. Patients in the more advanced stages of the disease (stage three and four) may experience a higher likelihood of recurrent TB episodes compared to those in the earlier stages (stage one and two), highlighting the importance of timely and effective management for patients with more advanced disease stages to reduce the risk of recurrence.

Age, diabetes comorbidity, hypertension comorbidity, and poor adherence to HIV medication were not found to be statistically significant factors associated with the recurrence of TB among HIV patients in the rural northeast, South Africa.

4.2 Time to another TB episode after successful treatment

The analysis of time to another TB episode after successful treatment provides valuable insights into the dynamics of TB recurrence in HIV patients on Antiretroviral Therapy (ART) in rural northeast, South Africa. The findings of this study show a diverse range of time intervals between initial TB episodes and subsequent recurrences, highlighting the heterogeneity of individual responses to treatment.

The minimum time to another TB episode observed in this study was remarkably short, at just 7 days (0.02 years). This rapid recurrence raises concerns about the potential challenges in effectively preventing TB recurrence in some patients, emphasizing the importance of continued post-treatment follow-up and targeted interventions in high-risk individuals. This finding aligns with other studies that have also reported rapid recurrence after successful TB treatment. For example, a study conducted by Moore et al. (2007) in Uganda found that some patients experienced TB recurrence within a few weeks of completing treatment (55).

The median time to another TB episode of 1.93 years observed in this study provides a critical reference point for estimating the time to recurrence. This value is in line with other studies that have reported median times to TB recurrence after successful treatment. For instance, a study by Houben et al. (2011) in a systematic review conducted to identify all studies on TB clustering and HIV infection in HIV-endemic populations, a median time to recurrence of 1.98 years was reported (56). This information is essential for clinical management and surveillance strategies, allowing healthcare providers to identify vulnerable periods and offer additional support to prevent recurrent TB effectively.

On the other end of the spectrum, the study observed a maximum time to another TB episode of approximately 8.66 years, suggesting the persistence of latent TB infection. This finding is consistent with research conducted by Marks et al. (2000), which reported that latent TB infection can remain dormant for many years before becoming active again (57). The prolonged latency periods underscore the importance of long-term monitoring and sustained efforts in maintaining treatment adherence to recurrence of TB.

The Kaplan-Meier Curves (Figures 3.1 to 3.8) provide visual representations of the risk of TB recurrence over time, stratified by various factors. The decreasing risk observed in these curves as time progresses indicates that the number of individuals at risk decreases over time. This finding is consistent with other studies that have shown a decrease in the risk of TB recurrence over time after successful treatment. For example, a study by Chiang et al. (2002) in Taiwan reported a decline in the risk of TB recurrence during the first two years after completing treatment (58). However, the decreasing risk also emphasizes the importance of early detection and targeted interventions during vulnerable periods to further reduce the risk of recurrent TB. Other studies have also highlighted the significance of early detection and interventions in preventing TB recurrence. For instance, a study by Lindiwe M. Faye et al. (2023) in South Africa emphasized the need for enhanced case finding and timely initiation of treatment to reduce the risk of recurrent TB and unfavourable outcomes (59).

An interesting observation is however made that patients with comorbidities are less likely over time to face a recurrence in TB than patients without comorbidities. This observation could

suggest that such patients with comorbidities were subjected to programmes that offered better and priority treatment to patients with comorbidities in particular. However, without statistical backing, it should be noted that these findings are purely observational and may require scrutiny in a further study to neatly establish the practicality of such phenomena.

4.3 Risk factors for recurrent TB among HIV patients on ART

The study identified several risk factors associated with recurrent TB among HIV patients receiving ART in the rural northeast. These factors include sex, WHO stage of HIV, baseline CD4 count, and the duration of previous TB treatment.

Male patients were found to be at a higher risk of experiencing recurrent TB compared to female patients. Other studies have reported similar findings. In study on risk factors associated with tuberculosis recurrences in South Korea, conducted by Hin Moi Youn et. al, it was found, in a cohort of 5,446 tuberculosis patients, that sex was a significant risk factor for TB recurrence. Male participants had a higher risk of experiencing TB recurrence compared to their female counterparts, with an adjusted hazard ratio (AHR) of 1.81 (95% CI: 1.11–2.94) (33). This finding suggests that being male is associated with an increased likelihood of TB recurrence. This could be because female have better health seeking behaviours than male (34). This finding emphasizes the need for targeted interventions to address this gender disparity and improve TB outcomes among male patients.

This study found that patients at stage 3 of the WHO HIV staging were at a significantly higher risk of experiencing recurrent TB compared to those at stage one. Ausman Ahmed et. al. (2017) reported similar findings. In their study, it was found that being in WHO clinical stages III and IV (AHR 2.84, 95% CI 1.11 - 7.27; AHR 3.07, 95% CI 1.08 - 8.75, respectively) was associated with a high risk of TB recurrence (60). This highlights the importance of early HIV diagnosis and effective management to prevent disease progression and reduce the risk of TB recurrence.

This study found that a higher baseline CD4 count is associated with a lower likelihood of TB recurrence. Similar findings were also reported by Lawn, Stephen D et. al. (2005) in a study titled “Tuberculosis among HIV-infected patients receiving HAART: long term incidence and

risk factors in a South African cohort"(35). In their study, it was found that a CD4 count of less than 100cells/mm^3 was associated with recurrent TB (ARR, 2.38; 95% CI, 1.01–5.60; P = 0.04) (35). Specifically, the current investigation demonstrated that individuals with a higher baseline CD4 count exhibited a reduced likelihood of experiencing TB recurrence. This crucial finding accentuates the pivotal role of maintaining a robust immune system, which can be achieved through early initiation of antiretroviral therapy and adherence to TB and HIV treatment, as pivotal strategies to mitigate the risk of TB recurrence in this population.

Patients with a longer duration of TB treatment were found to be at a higher risk of TB recurrence. Similar findings were reported by Mohammed Saif Anaam and Alian A. Alrasheedy (2023), in their study on recurrence rate of pulmonary tuberculosis in patients treated with the standard 6-month regimen it was shown that a standard six months TB treatment lowered the risk of TB recurrence, than a treatment duration of nine or twelve months which were associated with an increased risk of recurrent TB (44). On the contrary, Dick Menzies et. al. (2009), found that a shorter treatment duration of six months was associated with a higher risk of recurrent TB as compared to a nine – months treatment duration, and a twelve – months treatment duration (43). This difference can be because of disease severity or drug tolerance. The finding for this study suggests the need for continuous monitoring and support for patients during and after TB treatment to prevent recurrence.

4.4 Strengths and Limitations

The present study on risk factors for recurrent TB among HIV patients receiving ART in the rural northeast has several strengths that contribute to its credibility and value. Firstly, the study focused on a specific and relevant population, namely HIV patients in a rural setting, providing insights into a vulnerable group that might have limited access to healthcare resources. Additionally, the large sample size of 4803 subjects enhances the statistical power of the study, and lastly, the study employed survival analysis, a robust methodology for investigating time-to-event data, allowing for a comprehensive exploration of the risk factors and their association with recurrent TB.

However, like any research, this study also has certain limitations that should be considered when interpreting its results. Firstly, although the study identified several risk factors, other potentially relevant variables, such as viral load, line of treatments, height of patients (to measure BMI), socioeconomic status, and lifestyle factors like smocking status and alcohol consumption were not included. The absence of these variables may contribute to Furthermore, the study focused solely on a specific region, which may restrict the generalizability of the findings to other geographical areas or populations with different healthcare infrastructures and demographic characteristics.

Despite these limitations, the study provides valuable insights into the risk factors for recurrent TB among HIV patients who are on ART in a rural setting, which can inform targeted interventions and strategies to improve patient outcomes. Future research should consider addressing the identified limitations and conducting prospective studies with diverse populations to gain a more comprehensive understanding of the complex dynamics of recurrent TB among HIV patients. Overall, this study serves as a steppingstone for further investigations that could contribute to the global efforts to combat TB and HIV co-infection.

CHAPTER 5

5 Conclusion and Recommendations

5.1 Conclusion

This study has identified several significant risk factors associated with recurrent TB among HIV patients receiving ART in the rural northeast. Male patients were found to be at a higher risk of experiencing recurrent TB compared to female patients, emphasizing the need for targeted interventions to address this gender disparity and improve TB outcomes among male individuals. Additionally, patients at more advanced stages of HIV (WHO stage three and stage four) were at a significantly higher risk of TB recurrence, highlighting the importance of early HIV diagnosis and effective management to prevent disease progression. Maintaining a higher baseline CD4 count was associated with a lower likelihood of TB recurrence, underscoring the importance of early initiation of ART and adherence to HIV treatment to reduce the risk of TB recurrence. Furthermore, patients with a longer duration of TB treatment were found to be at a higher risk of recurrence, indicating the need for continuous monitoring and support during and after TB treatment to prevent future recurrences. These findings can provide valuable insights for healthcare providers and policymakers in developing targeted strategies to mitigate the risk of recurrent TB and improve the overall health outcomes of HIV patients in this region. Further research and collaboration between healthcare professionals are crucial in addressing these risk factors effectively and achieving better control of recurrent TB among HIV patients.

5.2 Recommendations

Based on the findings and limitations of the study on risk factors for recurrent TB among HIV patients receiving ART in the rural northeast, several recommendations can be made to enhance future research and inform public health interventions:

1. Gender-Specific Interventions: Given the higher risk of recurrent TB observed among male patients, targeted interventions should be designed to address this gender disparity. These interventions could focus on improving health-seeking behaviours among male individuals, enhancing access to healthcare services, and promoting early diagnosis and treatment.

2. HIV Early Detection and Immunological Support: Emphasize the importance of early HIV diagnosis and effective management to prevent disease progression and reduce the risk of TB recurrence. As it was seen in this study that some individuals had low baseline CD4 count – which may be because they were not diagnosed early. Efforts should also be made to provide immunological support to HIV patients. This may involve nutritional interventions, as it was discovered in this study, that some patients had low weight.

3. Continuous Monitoring and Support: Patients who undergo longer durations of TB treatment should be closely monitored and supported during and after the treatment period to prevent recurrence. Post-treatment follow-up programs should be established to detect any signs of TB recurrence early on.

4. Treatment Adherence Programs: As it was found in this study, that some patients were not adhering to their medication, there is a need to develop and implement treatment adherence programs that specifically address the challenges faced by patients in rural settings, such as transportation barriers or medication availability, to ensure patients complete their TB treatment successfully.

By addressing these recommendations, future research and public health efforts can contribute to a more comprehensive understanding of recurrent TB among HIV patients and facilitate the development of effective strategies to reduce its burden on affected communities.

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Appendices

Appendix A: Plagiarism declaration



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Kingsley Kanzoole (Student number: 2605424) am a student registered for the degree of MSc Epidemiology (IS) in the academic year 2023.

I hereby declare the following:

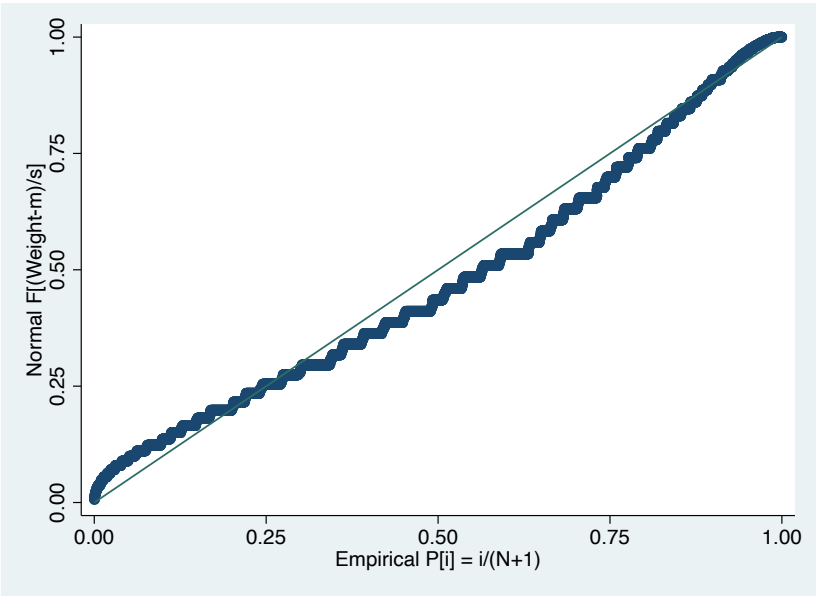
- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 11th September, 2023.

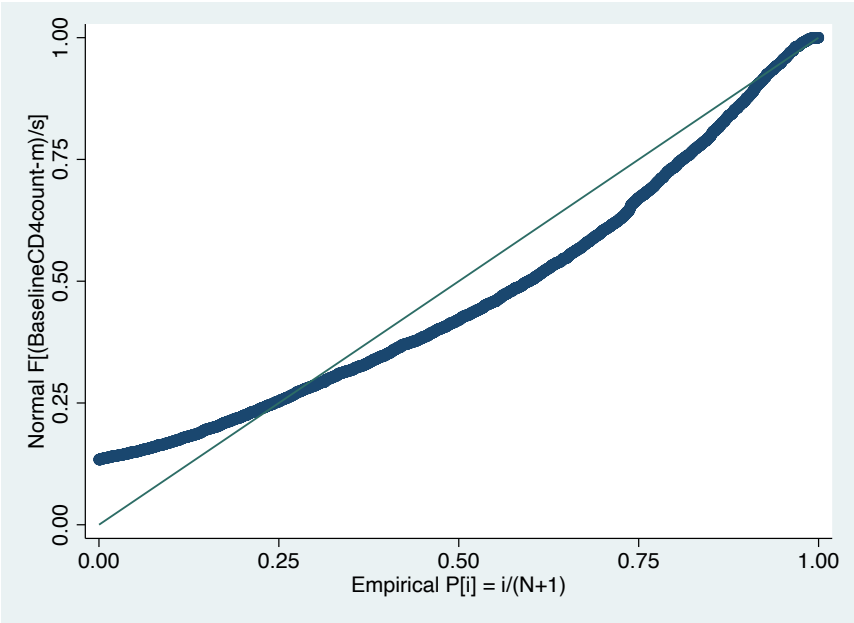
Appendix B: Power calculation Stata output

```
. power twoproportions 0.14 0.1, n1(1326) n2(3477)

Estimated power for a two-sample proportions test
Pearson's chi-squared test
H0: p2 = p1  versus  Ha: p2 != p1

Study parameters:

        alpha =    0.0500
            N =     4,803
           N1 =     1,326
           N2 =     3,477
        N2/N1 =    2.6222
        delta =   -0.0400  (difference)
           p1 =    0.1400
           p2 =    0.1000

Estimated power:

        power =    0.9688

.
end of do-file
```

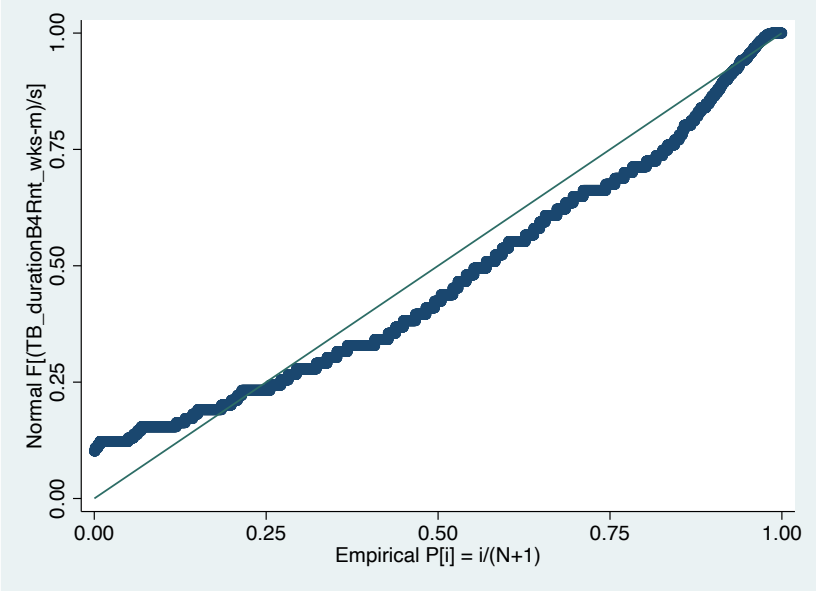
Appendix C: Normality test for variable, weight



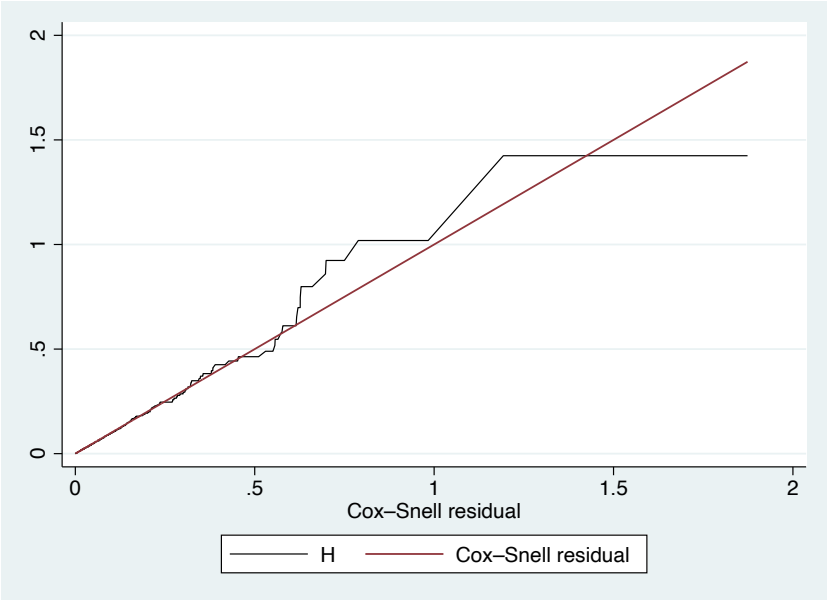
Appendix D: Normality test for variable, baseline CD4 count



Appendix E: Normality test for variable, duration of treatment of first TB episode



Appendix F: A graph plot for Cox-snell residuals



Appendix G: Turnitin Report

Satisfactory

KK_Research Report-4.docx

LATIFAT IBILOMI
18/09/2023

ORIGINALITY REPORT

9%	7%	6%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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6	pjmhsonline.com Internet Source	<1%

Appendix H: Ethics clearance certificate

M230409 MED23-02-201

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Mr Kingsley Kanzoole

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230409 MED23-02-201

NAME: (Principal Investigator)	Mr Kingsley Kanzoole
DEPARTMENT:	Epidemiology and Biostatics Division
PROJECT TITLE:	Risk factors for recurrent Tuberculosis among HIV patients who are on Anti-Retroviral treamnet in Rural Northeast, South Africa
DATE CONSIDERED:	05/05/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Latifat Ibisomi and Dr Chodziwadziwa Kabudula
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/05/2023 **EXPIRY DATE:** 30/05/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in April each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Login to upload signed copy of this ethics clearance certificate prior to commencing with the study https://www.witsethics.co.za/login.aspx

Principal Investigator Signature

05/06/2023
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix I: Permission to use data

MRC/Wits Rural Public Health and Health Transitions Research Unit
School of Public Health, Education Campus, 27 St Andrew's Road, Parktown 2193, South Africa
Telephone: +27 11 717 2085 (Johannesburg) +27 13 795 5076 (Acornhoek) www.agincourt.co.za

13th February 2023

To whom it may concern,

Authorisation to use the MRC/Wits Agincourt Research Unit data for a Master's degree research project

The reason for this letter is to authorize Mr. Kingsley Kanzoole, student number 2605424, to use the MRC/Wits Agincourt Research Unit data for the purpose of fulfilling the requirements for the **Masters in Epidemiology (Implementation Science)** with the title **"Risk Factors for Recurrent Episodes of Tuberculosis among HIV Patients in Rural Northeast, South Africa: A Retrospective Cohort Study"** in the Faculty of Health Science at the University of the Witwatersrand.

Mr. Kanzoole will have to fill in the Data Request form that can be found at the MRC/Wits Agincourt Research Unit's website to request which data is needed for her research project and the main objective of her work.

Please do not hesitate to contact us if you require further information.

Yours sincerely,



Prof. F. Xavier Gómez-Olivé (MD, PhD)
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MRC/Wits Rural Public Health and Health
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