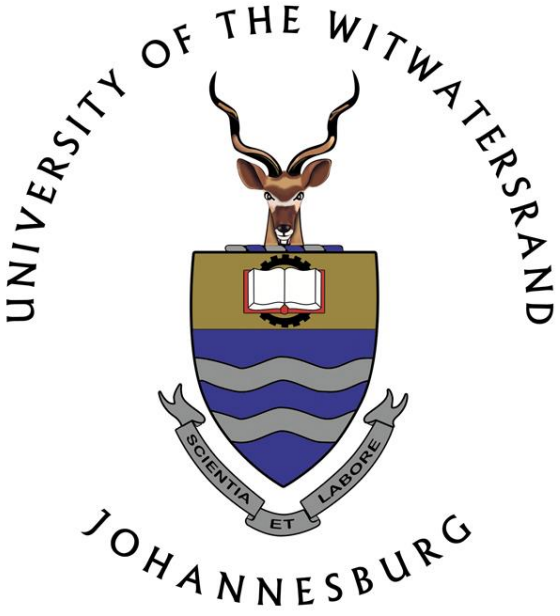

FACTORS ASSOCIATED WITH LOSS TO FOLLOW-UP IN HIV-UNINFECTED TUBERCULOSIS PATIENTS IN EKURHULENI NORTH SUB-DISTRICT

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MSc Epidemiology (Infectious Disease Epidemiology)

Johannesburg, November 2017

DECLARATION

I **Batanai Moyo** declare that this Research Report is my own, unaided work. It is being submitted for the Degree of MSc Epidemiology (Infectious Disease Epidemiology) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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3rd day of November 2017 in Johannesburg

For my mother who has always supported my dreams and believed in me.

ABSTRACT

Tuberculosis (TB) is a leading cause of death worldwide, causing more deaths than HIV/AIDS. A TB patient can have pulmonary or extrapulmonary TB or both. South Africa has a high incidence rate of TB, recording 834 cases per 100 000 population in 2015, compared to 142 per 100 000 globally. Loss to follow-up (LTFU) rates during TB treatment in South Africa have ranged from 7% to 30%.

The factors associated with LTFU can be divided into four groups: socioeconomic factors, patient-related factors, treatment factors, and health system or programmatic factors. Socioeconomic factors include a lack of support and a low socioeconomic status. Patient-related factors include substance abuse, beliefs and low TB knowledge, while treatment factors include side effects and a history of LTFU. Among health system or programmatic factors that contribute to LTFU are a poor relationship with the healthcare workers and large treatment programmes.

Studies to determine the factors associated with LTFU in HIV-uninfected TB patients are few as most studies have focused on HIV/TB co-infected patients. Co-infected patients make up almost 60% of TB patients. The aim of this study was to determine the demographic and clinical factors associated with LTFU in HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012. LTFU was defined as a lack of a documented treatment outcome among TB patients who should have completed TB treatment based on TB treatment start date.

The study was a retrospective cohort study involving the secondary analysis of routine TB treatment data collected from 18 primary care clinics in Ekurhuleni North sub-district. The

participants were described at the beginning of TB treatment using clinical and demographic data. The treatment duration and outcomes were also described. The burden of LTFU was determined. Univariate and multivariate logistic regression and Cox proportional hazards regression were used to determine the factors associated with LTFU. In addition, survival analysis was conducted to determine if there was a difference in the time to LTFU among HIV-uninfected TB patients based on clinical and demographic factors. Sensitivity analysis of the multivariate logistic regression and Cox proportional hazards regression was carried out to compare the results obtained when follow-up was restricted to 8 months to those obtained for 12 months of follow-up. Sensitivity analysis was also conducted around the definition of LTFU. The impact on the results of multivariate logistic regression after assuming that participants who had a missing treatment outcome in the primary study were not lost to follow-up was determined.

Five hundred and fifteen participants were included in the analysis. The median age of the participants was 33 years (IQR: 26-47). Fifty-eight percent of the participants were male. Pulmonary TB was the most common form of TB among the participants. The rate of treatment success was 77.67% and that of LTFU was 17.28%. Of those lost to follow-up, 60 had a missing treatment outcome and 29 had default as an outcome in the primary study. The median length of treatment was 6.39 months (IQR: 5.67-7.44), and the median time to LTFU was 3.67 months (IQR: 1.54-6.33). Eighty-two percent of the participants had a documented change of treatment phase. Clinics with a high patient burden had a similar proportion of poor outcomes (death, LTFU and treatment failure) to clinics with low patient burdens. Significant differences in change of treatment phase and length of treatment were observed between those lost to follow-up and those not lost to follow-up.

LTFU took place throughout TB treatment, with a steady increase in the probability of LTFU over the first 6 months of follow-up. None of the factors investigated had a significant effect on time to LTFU. Following logistic regression and Cox proportional hazards regression analyses, none of the factors assessed were significantly associated with LTFU. Sensitivity analysis showed that censoring the participants at 8 months did not change the results of the logistic regression analysis. For Cox proportional hazards regression, female participants had a 5% lower risk of LTFU compared to male participants in the 12-month analysis. In the 8-month analysis, female participants had a 5% higher risk of LTFU. When participants with a missing treatment outcome were not considered lost to follow-up, sex was found to be significantly associated with LTFU. Female participants had a 66% lower risk of LTFU compared to male participants.

A limitation of the use of secondary data in this study was that the study question asked in this study was different from the question that was asked in the primary study. As a result, the variables collected in the primary study were different from the variables required in this study. Information on socioeconomic status, residence type, comorbidities, treatment clinics and health system factors was not available.

None of the factors investigated in this study were significantly associated with LTFU in HIV-uninfected TB patients in Ekurhuleni North sub-district. The factors influencing LTFU in Ekurhuleni North may not have been investigated in this study. More studies need to be conducted with a wide range of variables in Ekurhuleni North to determine the factors that influence LTFU among HIV-uninfected TB patients.

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AIDS:	Acquired Immune Deficiency Syndrome
ART:	Antiretroviral therapy
BMI:	Body mass index
CI:	Confidence interval
DOTS:	Directly Observed Treatment, Short Course
EPTB:	Extrapulmonary tuberculosis
HIV:	Human Immunodeficiency Virus
HREC:	Human Research Ethics Committee
IQR:	Interquartile range
LTFU:	Loss to follow-up
MDR-TB:	Multidrug-resistant tuberculosis
TB:	Tuberculosis
WHO:	World Health Organisation
XDR-TB:	Extremely drug-resistant tuberculosis

CHAPTER 1: INTRODUCTION

1.1 Background

Tuberculosis (TB) is one of the leading causes of death, causing more deaths globally than the Human Immunodeficiency Virus (HIV) (Khan et al., 2016). TB is caused by *Mycobacterium tuberculosis* (Tola et al., 2015). TB can involve either the lungs (pulmonary TB) or other parts of the body (extrapulmonary TB (EPTB)). Approximately five to ten percent of those exposed to TB bacilli will develop TB disease at some point in their life, with differences in strain virulence, age, genetics and nutritional status accounting for differences in disease susceptibility (Neyrolles and Quintana-Murci, 2009). Poor people are disproportionately affected as they are exposed to poor living conditions and social deprivation that increase their risk of disease (Wood et al., 2010).

TB data is essential to quantify the burden of the disease to enable appropriate action to be taken. TB data is collected annually by the WHO from all of its member countries through national surveys and surveillance (WHO, 2016). Issues with data collection, particularly in remote areas, may result in underreporting. In South Africa, surveillance is good but can be compromised by incomplete information in different parts of the South African National TB Surveillance System (Podewils et al., 2015).

In 2015, there were 10.4 million new TB cases and 1.4 million deaths due to TB worldwide (WHO, 2016). An estimated 56% of TB cases were among men and 90% among adults (Chandra and Mishra, 2017). The global, African and South African TB incidence rates were 142, 275 and 834 cases per 100 000 population respectively in 2015 (WHO, 2016). Global and African statistics show that the mortality rate due to TB was higher in HIV-uninfected TB patients than in HIV-infected TB patients (WHO, 2016). The higher mortality rates in HIV-

uninfected TB patients may be due to HIV-uninfected patients not presenting for care as early as HIV-infected patients due to lower knowledge and less stigma. In addition, HIV-uninfected TB patients may not be prioritised in TB training programs. In South Africa, mortality was approximately 300% higher in HIV-infected TB patients compared to HIV-uninfected patients (WHO, 2016). The overall TB mortality rate in South Africa was 179 deaths per 100 000 population, compared to 24 and 75 deaths per 100 000 population worldwide and in Africa respectively in the same year (WHO, 2016).

Previous studies in South Africa have found that LTFU ranged from 7% to 30%, with rates higher than 20% being observed in studies involving patients with drug-resistant TB (Brust et al., 2010, Gafar et al., 2014, Kendall et al., 2013, Kigozi et al., 2017, Pepper et al., 2012). In 2015, treatment success rates in South Africa stood at 78%, which was lower than the African and worldwide rates of 81% and 83% respectively (WHO, 2016). Approximately 1.8% of the new cases and 6.7% of the retreatment cases were multidrug-resistant TB (MDR-TB) cases (WHO, 2015).

Successful TB treatment is crucial to decrease the burden of TB as unsuccessful TB treatment will result in increased contact rates in communities which will in turn fuel the spread of TB. The Directly Observed Treatment, Short Course (DOTS) strategy is the main TB treatment strategy used in South Africa (Kigozi et al., 2017), and has been in use since 1997 (Churchyard et al., 2014). The strategy, which is efficient and cost effective, is recommended globally for TB control programmes (WHO, 2017b).

DOTS has five components: continuous financial commitment and political will, the use of sputum-smear microscopy for diagnosis, the administration of a standardised short course of

TB treatment with supportive and direct observation, a constant stock of high quality anti-TB drugs and the standardisation of case recording and reporting to monitor individual and programme performance (WHO, 2017a, WHO, 2017b). The goals of DOTS are to ensure that patients complete TB treatment and to stop the development of drug resistance in communities (Davies, 2003). Through ensuring an effective drug supply and management system, DOTS helps to ensure that national TB programmes do not have to deny patients care due to inadequate drug stocks (WHO, 2017b).

Isoniazid, rifampicin, pyrazinamide and ethambutol are the first-line drugs used for the treatment of drug-susceptible TB (Kasozi et al., 2015). TB treatment involves two months of intensive therapy using pyrazinamide, isoniazid, rifampicin, and ethambutol, followed by a continuation phase (four months) using rifampicin and isoniazid (Budgell et al., 2016). In severe or complicated cases of EPTB, the continuation phase may last for seven months (SA Department of Health, 2014). A new, shorter regimen for the treatment of MDR-TB lasts nine to twelve months unless there is resistance to second line drugs (WHO, 2016). Treatment for extremely drug-resistant TB (XDR-TB) lasts for 24 months (Caminero et al., 2010).

According to the WHO, TB treatment outcomes can be cure and treatment completion (classified as treatment success or ideal outcomes), or treatment failure, death and lost to follow-up (classified as bad outcomes), or not evaluated, which are described below for treatment in patients with drug susceptible TB (WHO, 2014):

- **Cure**: Occurs when a patient starts treatment with bacteriological confirmation of disease and is smear or culture negative in the final treatment month and on a minimum of one previous occasion.

- **Treatment completion**: Occurs when a patient completes his/her treatment with no sign of being unsuccessful and sputum test results are unavailable.
- **Treatment failure**: Occurs when a patient's smear or culture is positive at any point from five months after the start of treatment.
- **Death**: Death due to any cause while undergoing TB treatment.
- **Lost to follow-up**: Occurs when a patient either does not begin treatment or has his/her treatment interrupted for at least two consecutive months.
- **Not evaluated**: Occurs when the treatment outcome is not assigned. This may be due to the patient transferring to a different treatment facility or the outcome being unknown.
- **Treatment success**: Treatment success is the sum of cure and treatment completion.

In South Africa, the definitions of treatment outcomes used in the TB programme are similar to those provided by the WHO, with some minor differences, and are described in the National Tuberculosis Management Guidelines 2014 document (SA Department of Health, 2014). The definitions given by the WHO are for all bacteriologically confirmed and clinically diagnosed TB cases (WHO, 2014). On the other hand, those in the South African guidelines are split into 2 groups: the first for patients with smear or culture positive pulmonary TB, and the second for patients with smear or culture negative pulmonary TB and patients with extra-pulmonary TB (SA Department of Health, 2014).

The South African guidelines state that a cured patient should test smear or culture negative at least 30 days prior to the final test in the final month of treatment (SA Department of Health, 2014), while the WHO does not state the amount of time required between the two tests (WHO, 2014). In South Africa, patients who develop drug resistant TB during treatment should be

assigned the outcome ‘treatment failure’ (SA Department of Health, 2014), while the WHO states that when analysing treatment outcomes these patients should be included in the second-line TB treatment analysis group instead of the main TB cohort (WHO, 2014).

The South African guidelines define treatment default, which according to the definition used can only occur during treatment (SA Department of Health, 2014), whereas the WHO defines LTFU, which can occur before treatment begins or during treatment (WHO, 2014). The outcome ‘not evaluated’ is not included in the South African guidelines, but ‘transfer out’ is used instead (SA Department of Health, 2014). Transfer out is defined as “Patient who was referred to a facility in another district to continue treatment and for whom the treatment outcome is not known” (SA Department of Health, 2014).

To help the country meet the WHO target of ending TB by 2035, South Africa has adopted the Stop TB’s Global Plan to End TB (Kigozi et al., 2017). The goals of the plan include reducing the total number of TB deaths by 90% and the incidence of TB by 80% by 2030 compared to 2015 (WHO, 2016).

1.2 Literature review

Studies have found several factors that contribute to LTFU in TB patients (Garrido et al., 2012, Ifebunandu and Ukwaja, 2012, Kigozi et al., 2017, Shringarpure et al., 2015, Tola et al., 2015, Tupasi et al., 2016). In these studies, LTFU was defined as the interruption of TB treatment for at least two months. Factors influencing LTFU can be divided into four main groups: socioeconomic factors, other patient-related factors, treatment factors and health system or programmatic factors (SA Department of Health, 2014, Shringarpure et al., 2015). All the studies cited in this literature review involved both HIV-infected and uninfected TB patients,

except for the studies by Prado *et al*. (2017) and Satti and Kondagunta (2016) which involved HIV-infected TB patients only.

While most of the studies were cohort studies, some authors used the case-control study design where age and sex were matched (Roy et al., 2015, Satti and Kondagunta, 2016), unmatched case-control study design (Culqui et al., 2012, Finlay et al., 2012, Hasker et al., 2008, Holtz et al., 2006, Tupasi et al., 2016), meta-analysis and systematic review (Toczek et al., 2013) and mixed methods (Chida et al., 2015, Sanchez-Padilla et al., 2014).

In the review below, factors affecting LTFU outside South Africa are given first, then the factors influencing LTFU in South Africa are discussed.

1.2.1 Socioeconomic factors

Several studies have been conducted globally to determine the socioeconomic factors associated with LTFU. A lack of social support was found to be a predictor of LTFU, for example, if patients did not have somebody to go with them to the treatment clinic during the intensive treatment phase (Shringarpure et al., 2015, Tola et al., 2015). In one study, patients who experienced LTFU were likely to have small families, live alone and have a separated or disrupted marital status (Satti and Kondagunta, 2016). The presence of one or more of these factors may mean that a patient has reduced support and encouragement during TB treatment which may increase the risk of LTFU. These patients may also have lower levels of motivation during treatment. In many instances, the nature of TB treatment (the duration and the large number of drugs) is not consistent with a TB patient's belief system, culture or living circumstances, so without an adequate support system, LTFU would probably occur (TB CARE I, 2014).

A lower socioeconomic level, unemployment, being a pensioner and the absence of transport money contributed to LTFU in TB patients (Hasker et al., 2008, Shringarpure et al., 2015). In settings where patients were responsible for paying for their treatment, the cost of TB treatment contributed to LTFU (Toczek et al., 2013). Although the cost of treatment for one TB patient in South Africa can be as high as US$26 392 (Pooran et al., 2013), TB diagnosis and treatment are provided free of charge in South Africa (Foster et al., 2015). Patients, however, still have many direct and indirect costs that average US$111.83 and US$212.24 respectively (Foster et al., 2015). The costs include nutritional supplements, transport and carer costs (Foster et al., 2015). These costs may influence unemployed TB patients or those with a lower SES to discontinue TB treatment.

Shringarpure *et al*. (2015) found that the lower the level of education attained by a patient, the more likely the patient is to be lost to follow-up. Akessa *et al*. (2015) found that living in a rural area and a change of residence during treatment were associated with LTFU. A study by Tupasi *et al*. (2016) found that residence in an urban slum significantly increased LTFU. This may be due to the difficult socioeconomic conditions, such as inadequate housing and limited access to healthcare and other services, found in slums (Kizito et al., 2011). The mobile nature of the population, likely fuelled by the poor living conditions, may also exacerbate LTFU (Kizito et al., 2011).

Socioeconomic factors influencing LTFU in South Africa include living in rural areas, not owning a radio, being born outside of South Africa, migration and not having time to go to the treatment clinic (Holtz et al., 2006). Immigrants have been found to struggle to understand the treatment, increasing the likelihood of LTFU (Caylà et al., 2009). In addition, LTFU among migrants may occur due to fear of deportation, anti-migrant sentiments, low incomes, lack of

access to care and information (IOM, 2013, IOM, 2014). South Africa has a high number of migrants, both internal and external, and this may drive LTFU. Ekurhuleni may be a popular district for migrants to settle in on arrival in Gauteng due to a lower cost of living in the district.

One study found that TB patients with a formal salary had higher rates of LTFU than patients that relied on family and social contributions (Peltzer and Louw, 2014). This may be due to the fact that employment has been found to influence LTFU for many reasons, including patients not wanting their co-workers to know that they were ill and employers not allowing patients time off or paid sick leave (Finlay et al., 2012). A lack of formal education, working as a labourer and taking treatment without eating (due to a lack of food) increased the risk of LTFU (Finlay et al., 2012).

1.2.2 Other patient-related factors

Many studies conducted worldwide have investigated the effects of patient-related factors on LTFU during TB treatment. Using tobacco during TB treatment was significantly associated with LTFU (Dooley et al., 2011, Kuchukhidze et al., 2014). While some authors have found that LTFU is more likely to occur in men and in older patients (Ifebunandu and Ukwaja, 2012, Sanchez-Padilla et al., 2014), others found that a patient's sex and age have no influence on LTFU (Akessa et al., 2015, Kuchukhidze et al., 2014). A study in Brazil found that black TB patients were more likely to experience LTFU than any other race (Prado et al., 2017).

Incarceration, whether previous or current, was found to influence LTFU during TB treatment (Kuchukhidze et al., 2014, Sanchez-Padilla et al., 2014). Kuchukhidze *et al*. (2014) did not find BMI to be associated with LTFU, whereas Shringapure *et al*. (2015) found that patients with a low BMI were most likely to experience LTFU. A low BMI can be an indicator of other factors

that may influence LTFU such as a low socioeconomic status, inadequate access to healthcare and co-morbidities.

A low general knowledge about TB increased the likelihood of LTFU (Tupasi et al., 2016). Patients who were lost to follow-up were found to not know the duration of treatment (Putera et al., 2015). Pre-existing pulmonary disease (Garrido et al., 2012) and psychiatric disorders (Toczek et al., 2013) were found to increase the risk of LTFU. In addition, community beliefs were found to influence LTFU (Ade et al., 2016), for example, some communities believed that TB treatment would make them sterile (Chida et al., 2015). HIV testing was found to be protective against LTFU (Lackey et al., 2015).

In South Africa, a study found that older patients were more likely to be lost to follow-up than younger ones (Gafar et al., 2014). Smoking marijuana and mandrax during TB treatment, as well as spending time in prison had a negative effect on LTFU in TB patients (Holtz et al., 2006). A study found that the use of illicit drugs has been increasing in Gauteng (Mushayabasa and Tapedzesa, 2015). Drugs may influence TB patients to make poor decisions, which may lead to LTFU. The combination of the illicit drugs and TB medication may also worsen side effects of medications and force patients to abandon care. Feeling ashamed of the TB diagnosis and visiting a traditional healer were found to significantly increase LTFU (Finlay et al., 2012). Patients with an unknown HIV status were 30% more likely to be lost to follow-up than patients who were HIV-uninfected (Kigozi et al., 2017).

1.2.3 Treatment factors

Hasker *et al*. (2008), Ifebunanda and Okwaja (2012) and Roy *et al.* (2015) found that most patients who were lost to follow up were lost to follow-up during the intensive phase of TB

treatment. On the other hand, Akessa *et al*. (2015) and Kuchukhidze *et al*. (2014) found that most patients who were lost to follow up were lost to follow-up in the continuation phase. Side effects from the medication were reported as a common cause of LTFU (Hasker et al., 2008, Roy et al., 2015, Shringarpure et al., 2015, Tola et al., 2015). Side effects due to TB treatment include nausea, joint pain, abdominal cramps, dizziness, peripheral neuropathy, and hepatotoxicity (Arbex et al., 2010).

Kuchukhidze *et al*. (2014) observed that previous treatment was significantly associated with LTFU while Sanchez-Padilla *et al*. (2014) and Akessa *et al*. (2015) did not find a significant association. Tola *et al.* (2015) found that the likelihood of LTFU increased if symptoms decreased. Pulmonary TB, culture conversion, smear status, the drug-resistance status of the bacteria and the number of treatment interruptions were found to be significantly associated with LTFU (Kuchukhidze et al., 2014, Sanchez-Padilla et al., 2014). Patients receiving treatment for MDR-TB were more likely to be lost to follow-up than those with drug-sensitive TB (Lackey et al., 2015). In India, missing 5 or more treatment doses increased the risk of LTFU (Roy et al., 2015).

In South Africa patients were more likely to be lost to follow-up if the treatment did not relieve their symptoms (Holtz et al., 2006, Finlay et al., 2012). Patients who had a history of LTFU from treatment had a higher likelihood of LTFU (Gafar et al., 2014).

1.2.4 Health system or programmatic factors

The literature is clear that the relationship between a patient and the healthcare provider is important in preventing LTFU during TB treatment. Patients who did not have a good relationship with the health care workers at the treatment centres were more likely to be lost to

follow-up (Roy et al., 2015, Tola et al., 2015). Common problems encountered were patients not being happy about the healthcare worker's attitude towards them, a lack of trust in and support from the health care workers, and poor communication (Tola et al., 2015, Tupasi et al., 2016). Patients who received little assistance from the health facility during treatment had a high likelihood of LTFU (Tupasi et al., 2016).

An association between increased rates of LTFU and large programme sizes and drug stock-outs was found (Toczek et al., 2013). Standardising treatment regimens and providing financial and nutritional support to patients resulted in a reduction in LTFU, but the use of legal action to force patients to adhere to treatment did not make a difference (Toczek et al., 2013). Patients were more likely to be lost to follow-up if they received treatment at a government treatment facility than patients who received treatment at a community facility (Roy et al., 2015). Private treatment facilities were also found to be protective against LTFU (Sitienei et al., 2015). Long waiting times, the need for repeated visits and delays in obtaining test results resulted in increased rates of LTFU (MacPherson et al., 2014).

In South Africa, healthcare system factors associated with LTFU include long waiting periods for culture test results and delayed treatment initiation (Padayatchi et al., 2014). Drug stock-outs and shortages have also been implicated in treatment LTFU (Padayatchi et al., 2014, Seunanden and Day, 2014). Poor relationships with healthcare workers contributed to LTFU (Holtz et al., 2006). Insufficient education on TB treatment, not being told that treatment lasts at least 6 months and feeling as though the provision of food by healthcare workers during TB treatment would help the patient finish their treatment contributed to patients not adhering to TB treatment (Finlay et al., 2012).

Treatment in community healthcare centres was found to influence LTFU (Gafar et al., 2014). In general, the inadequate number of healthcare professionals and an overburdened healthcare system in South Africa have contributed to LTFU during TB treatment as the standard of care has been reduced by these factors (Finlay et al., 2012). Poor follow-up systems and mismanaged treatment programmes have been found to influence LTFU (Kigozi et al., 2017). Finlay *et al*. (2012), found that DOTS did not make a difference to LTFU rates as half of the patients on DOTS reported that they did not take their medication under direct supervision. The lack of supervision may be caused by the shortage of healthcare workers or by unmotivated healthcare workers due to the state of the healthcare system. Inconvenient clinic hours were also associated with increased LTFU during TB treatment (Finlay et al., 2012).

1.3 Problem statement

A search of the literature shows that most work that has been done to determine the factors influencing LTFU in South Africa has been done in HIV/TB co-infected patients. Approximately 57% of TB patients in South Africa are infected with HIV (Massyn et al., 2016). As a result, there is a knowledge gap of the factors influencing LTFU in the remaining 43% of TB patients who are HIV-uninfected.

The patterns of TB disease are different in HIV-infected and HIV-uninfected patients, for example, HIV-infected patients are more likely to have EPTB (Fenner et al., 2012, Gebremariam et al., 2016) and acid-fast smear-negative TB (Sterling et al., 2010). Acid-fast smear-negative TB is active TB that gives a negative result when a smear test is done using a rapid test. Furthermore, HIV-infected TB patients have a high pill burden and drug interactions (Sterling et al., 2010). Death during TB treatment is more common in HIV-infected patients

than in HIV-uninfected patients (Mohr et al., 2015). Side effects, however, have been found to be similar in both HIV-infected and uninfected TB patients (Shean et al., 2013).

The differences in the patterns of TB disease mentioned above are likely to influence differences in patterns of LTFU between the two groups. Studies to determine the factors influencing LTFU in HIV-uninfected TB patients are required as very few have been conducted in South Africa. In addition, no studies that focused on 'outcome not evaluated' were found during the literature search.

1.4 Justification

Knowledge of the factors that influence LTFU during TB treatment is important as patients who are lost to follow-up have a high risk of spreading the infection to their contacts, developing drug resistant TB and dying (Akessa et al., 2015, Kuchukhidze et al., 2014). A study conducted in Peru found that about 50% of patients who were lost to follow-up during TB treatment did not survive for more than 3 years after LTFU (Toczek et al., 2013). In Brazil, the death rate among patients who were lost to follow-up was 4.2 times higher than the death rate in patients who were not lost to follow-up (Cunha et al., 2017). Patients who were lost to follow-up early-on had a higher risk of death than those that were not (Cunha et al., 2017). The financial burden on the healthcare system is increased when adherence to TB medication is low (Lackey et al., 2015).

Patients who transfer out during TB treatment and whose outcome is unknown by the sending clinic are normally assigned the outcome 'treatment not evaluated' (Takarinda et al., 2012). These patients can be considered to be lost to follow-up. Transfer during TB treatment has been linked to a reduction in treatment compliance which increases the risk of LTFU (Belayneh et

al., 2016). The results obtained in this study will help inform interventions and efforts to reduce LTFU in HIV-uninfected TB patients in South Africa.

1.5 Study Question

What demographic and clinical factors are associated with LTFU during TB treatment among HIV-uninfected TB patients from Ekurhuleni North sub-district who registered for TB treatment from 1st January 2011 to 30th June 2012? LTFU was defined as a lack of a documented treatment outcome among TB patients who should have completed TB treatment based on TB treatment start date. Patients who were lost to follow-up and interrupted treatment (previously described as default) and those who were lost to follow-up but not successfully traced (outcome not evaluated) were assigned the outcome LTFU. Since there were no records of any participants transferring out during TB treatment, no study participants were assigned the outcome LTFU based on transfer out.

1.6 Aim

To determine the demographic and clinical factors associated with LTFU in HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012. The patients were followed up until the end of treatment or until data were collected from November 2012 to June 2013.

1.7 Objectives

1. To describe the clinical and demographic characteristics of HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012.

2. To determine the burden of LTFU among HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012.
3. To determine the clinical and demographic factors associated with LTFU in HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012.
4. To determine if there is a difference in time to LTFU among HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012 based on clinical and demographic factors.

CHAPTER 2: METHODS

This chapter presents the materials and methods used in this study. The study design, study population, study site, primary study, sampling method, data cleaning, variables used and data analysis are described here.

2.1 Study design

This study was a retrospective cohort study. The study involved secondary data analysis of data collected during a study entitled "Evaluation of the detection, management and outcomes of TB and TB treatment outcomes at 18 primary care facilities in Ekurhuleni North sub-district."

2.2 The primary study

The primary study was a retrospective cohort study based on record review and abstraction. The study was conducted at 18 primary care clinics in Ekurhuleni North sub-district. The overall objective of the study was to evaluate case detection, management and treatment outcomes among HIV-infected and uninfected TB patients who registered for TB treatment at the clinics during the period 1st January 2011 to 30th June 2012. The clinics were selected for the study from a total of 32 primary care clinics in Ekurhuleni North because they offered TB diagnosis and treatment services, had no other research activities and had sufficient numbers of patients for the study.

Data were collected from the TB treatment registers and other clinic records such as clinic cards and the antiretroviral therapy (ART) register. Demographic variables, TB diagnostic methods variables and TB treatment and management variables were collected. The data collected had been compiled over the duration of TB treatment as participants went to the treatment clinics for regular appointments. Record review and abstraction (data collection for

the primary study) began in November 2012 and ended in June 2013. In total, 2 971 patients were enrolled in the primary study. The results of the study were used to assist with the planning of a TB/HIV integration project as well as TB treatment and vaccine trials in Ekurhuleni North sub-district.

2.3 Study site

The study site comprised 18 clinics offering primary health care in Ekurhuleni North sub-district. Ekurhuleni North sub-district is located in the Ekurhuleni Metropolitan Municipality, Gauteng Province, South Africa (Statistics South Africa, 2016). In 2016, Ekurhuleni had a population of 3.2 million people (Statistics South Africa, 2016). The TB treatment success rate was 87.2% in 2012 (Massyn et al., 2014). In 2015, there were 298 incident cases of TB per 100 000 population in Ekurhuleni, with a treatment success rate of 85.6%, and a death rate of 5.6% (Massyn et al., 2016). Between 2009 and 2014, TB was the most common cause of death among 15-64 year olds in Ekurhuleni (Massyn et al., 2016). Sixty-eight percent of TB patients in Ekurhuleni were HIV positive in 2015 (Massyn et al., 2016).

2.4 Study population

The study population consisted of 515 HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district between 1st January 2011 and 30th June 2012. Participants should have completed TB treatment based on TB treatment start date by the time the data were collected for the primary study to be included in the study. All study participants were adults aged 18 years and above at the start of TB treatment. No patients with drug resistant TB were included in the study as treatment for drug resistant TB was not provided at the clinics during the treatment registration period.

2.5 Sampling

A sub-sample of the original data was selected by excluding the HIV-infected patients in the study. The StatCalc command in EpiInfo 7 was used to calculate the sample size. The sample size required for this study was 59 and 88 at the 80% and 90% power levels respectively. With 515 HIV-uninfected participants in the study, the dataset was large enough for the study. The assumptions made were that, on average, 11% of patients are lost to follow-up during TB treatment in Johannesburg (Budgell et al., 2016), the acceptable margin of error was 5% and the design effect was 1.

2.6 Methods for measuring outcomes

The main outcome was LTFU. Patients whose treatment outcomes in the primary study were recorded as default or unknown/no record or were missing were considered lost to follow-up. The participants with the remaining treatment outcomes (cured, treatment completed, MDR-TB, died and failure) were considered to not be lost to follow-up.

The length of treatment was calculated as follows: date of treatment completion minus date of treatment commencement for patients who completed TB treatment, and date of most recent clinic visit minus date of treatment commencement for patients who were either lost follow-up or died during treatment. The length of treatment was calculated in months.

A participant was said to change treatment phase when he/she went from the intensive phase to the continuation phase. Time to change of treatment phase was calculated by subtracting the date treatment began from the date of change of treatment phase. The time to change of treatment phase was calculated in months.

2.7 Data management and analysis

2.7.1 Data cleaning

The software used in this study was STATA 14. The dataset had 2 971 participants, composed of HIV-infected and uninfected participants. Participants who had missing, positive or unknown HIV results were excluded from the study. Some of the records were duplicated. The observations that were kept in the study were the ones with the outcome recorded. Where both observations had an outcome, the latest recorded observation was kept. Participants who were still receiving treatment when the data were collected were excluded from the study. The final number of participants in the study was 515.

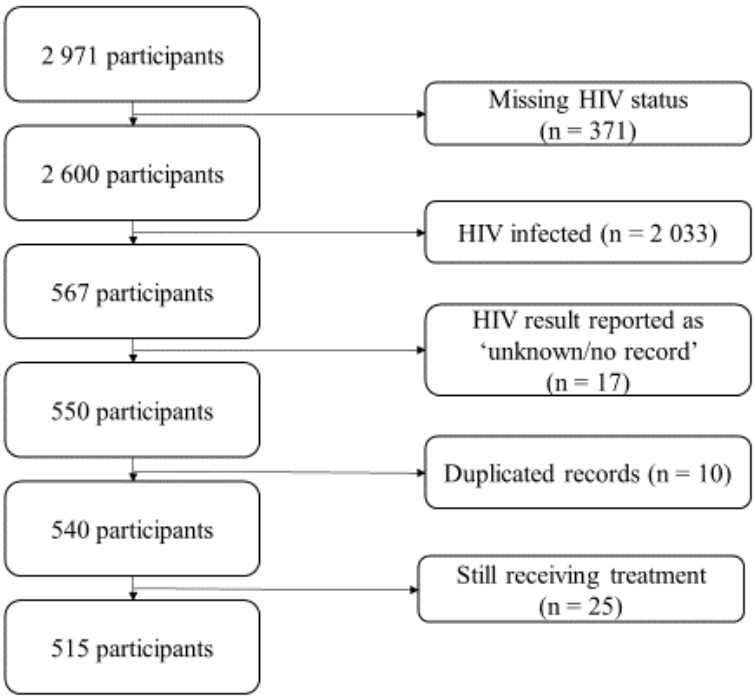

Figure 2.1: Flow chart showing participant eligibility criteria

The variables used in the study is described in Table 2.1 below. The coding used for all the variables used in the project is given in the Appendix in Table A1.

Table 2.1: Description of the variables used in the study

Variable	Description
Participant ID	The participant IDs in the primary study were in the form 'Protocol-Site code-Participant ID'. Unique, numerical identification numbers were assigned to all participants to increase the ease of data cleaning.
Treatment clinic	The treatment clinic was obtained from the participant IDs given in the primary study.
Age at TB diagnosis	Categorised into 18-34 years and 35+ years. The median age of the participants was 33 years, so the two age categories were created based on this value while ensuring that participants were relatively equally distributed between the two.
Patient burden at treatment clinic	The clinics were classified as having a low or high patient burden depending on the number of HIV-uninfected TB patients treated. Clinics that had 40 or more HIV-uninfected TB patients were classified as having a high patient burden.
TB treatment outcome	This variable was created to take into account the definition of LTFU used in this study. Participants with unknown/missing and default as treatment outcomes in the primary study were assigned LTFU as their outcome in this study. Participants who had a missing outcome were also assigned LTFU as their treatment outcome. The treatment outcomes in the new treatment outcome variable were treatment success (which was the sum of cured and completion), LTFU, MDR-TB, death and treatment failure. There was no information on patient transfer during treatment.
Success or poor treatment outcome	Treatment outcomes were classified as success or poor outcomes. Successful treatment outcomes were cured and completion. Poor treatment outcomes were LTFU, MDR-TB, death and treatment failure.
Date variables	New date variables in STATA format were created. These variables were treatment start date, date of change of treatment phase, date of most recent clinic visit and date of treatment completion.
Date of treatment exit	For participants who were either lost to follow-up or had died, the exit date was the date of the most recent clinic visit. The date of completion of TB treatment was the exit date for participants who completed TB treatment.
Time to LTFU	The time to LTFU was calculated in months using the date of most recent clinic visit minus the date treatment began.

2.7.2 Data analysis

The purpose of this section is to describe the statistical analysis methods used to complete each objective.

- *Objective 1: To describe the clinical and demographic characteristics of HIV-uninfected TB patients.*

The variables were divided into two groups: demographic and clinical variables at the start of TB treatment and variables describing TB treatment duration and outcomes. The variables used to describe the participants at the start of treatment were age at TB diagnosis, sex, episode type, TB site, smear and culture status and patient burden at treatment clinic. Age was used in its continuous and categorical forms while the remaining variables were categorical. The continuous variables used to describe the treatment duration and outcomes were length of treatment, time to LTFU and time to change of treatment phase. The categorical variables were change of treatment phase, treatment outcome, LTFU, length of treatment, time to LTFU and time to change of treatment phase.

The median and interquartile range (IQR) were calculated for the continuous variables. Proportions were calculated for the categorical variables. Treatment outcome by treatment clinic and by patient burden at treatment clinic were determined. The treatment outcomes were grouped into success and poor outcomes for these analyses.

- *Objective 2: To determine the burden of LTFU among HIV-uninfected TB patients.*

The outcome variable was LTFU. The variables used were age at TB diagnosis, length of treatment, time to change of treatment phase, sex, episode type, change of treatment phase, patient burden at treatment clinic and TB site, smear and culture status. The proportion of

participants with LTFU was determined for each independent variable. The median and IQR were calculated for each category (except unknown/missing) for age at TB diagnosis, length of treatment and time to change of treatment phase. The proportions and p-values were calculated for the categorical variables. The chi-squared test, conducted at the 5% significance level, was used to calculate the p-values.

- *Objective 3: To determine the clinical and demographic factors associated with LTFU in HIV-uninfected TB patients*

The outcome variable was LTFU. The variables used were age at TB diagnosis, sex, episode type, patient burden at treatment clinic and TB site, smear and culture status (all categorical). Logistic regression modelling was used as the outcome was binary. Univariate analysis was conducted to test the association between each factor and LTFU. The p-values, odds ratios and 95% confidence intervals (CI) were obtained.

For multivariate analysis, multiple logistic regression modelling was used. A p-value cut-off of 0.2 was used to select variables for multivariate analysis. Age and sex were included *a priori*. The p-values, odds ratios and 95% CI were obtained. Confounding and interaction were investigated. To be considered a confounder, a variable needed to change the odds ratio of another variable by 10% after adjusting for it. The likelihood ratio test was used to test if interactions improved the model obtained. A test of goodness of fit was conducted to test the goodness of fit of the model obtained. For both univariate and multivariate analysis, the level of statistical significance was 5%.

- *Objective 4: To determine if there is a difference in time to LTFU among HIV-uninfected TB patients based on clinical and demographic factors*

The date variables used were treatment start date and exit date. The categorical variables were age at LTFU, age at TB diagnosis, sex, episode type, TB site, smear and culture status, and patient burden at treatment clinic. The failure event was LTFU. The origin was the date that TB treatment began, and participants would exit on or before the failure event.

The Kaplan-Meier method was used for survival analysis. The number of events (LTFU), incidence rate, 95% CI and p-value were obtained. The incidence rate was obtained per 100 person-months as the length of TB treatment was in months. The log-rank test was used to test for a statistically significant association between the variables and time to LTFU at a 5% significance level. A graph of the Kaplan-Meier failure estimate was generated.

Cox proportional hazards regression was used identify factors associated with LTFU. Univariate and multivariate analyses were conducted. Factors that had been used in multivariate logistic regression were used for the multivariate Cox proportional hazards regression, regardless of the p-value in univariate analysis. Confounding and interaction were investigated, and a test of proportional hazards assumption was conducted.

2.8 Sensitivity analyses

Analyses 1 and 2

Sensitivity analyses were conducted to determine if censoring participants after eight months of treatment had any effect on the results of the multivariate logistic regression and Cox proportional hazards regression analyses. The data were censored at eight months because TB treatment normally lasts six to eight months.

Analysis 3

Sensitivity analysis was also conducted around the definition of LTFU. Multivariable logistic regression analysis was conducted where participants with a missing outcome were assumed to have been followed up elsewhere, so that only the participants with default as an outcome in the primary study were considered to be lost to follow-up in this study.

2.9 Ethics

The primary study received ethics clearance from the Human Research Ethics Committee (HREC) (Medical) at the University of the Witwatersrand (certificate number M120830). For this study, permission to use the data was obtained from the Aurum Institute. Ethics clearance was obtained from HREC (Medical) at the University of the Witwatersrand (certificate number M161183).

CHAPTER 3: RESULTS

This chapter will present the results obtained during this study. In total, 515 participants were eligible for the study. The demographic and clinical characteristics of the participants and the burden of LTFU are described. The results of the logistic regression, time to event analysis, Cox proportional hazards regression and sensitivity analyses are also presented.

3.1 Description of the clinical and demographic characteristics of the study participants

Table 3.1 presents the results of the descriptive analysis of the participants' demographic and clinical data at the start of TB treatment. The median age at TB diagnosis was 33 years (IQR: 26-47). Just over half of the participants (53.40%) were aged between 18 and 34 years. The majority of the participants (58.09%) were male. More than 90% of the participants had a new TB episode. Almost 48% of the participants had pulmonary TB that was smear or culture positive. There was a fairly even distribution of the remaining participants between pulmonary smear and culture negative TB, and non-pulmonary TB. More participants were treated at clinics that had a low patient burden (less than 40 HIV-uninfected TB patients) than at clinics that had a high patient burden. Five of the 18 clinics had a high patient burden.

Table 3.1: Demographic and clinical characteristics of the study participants at the start of TB treatment

Variable	**Median (IQR)**
Age at TB diagnosis (years)	33 (26-47)
Variable	**N (%)**
Age at TB diagnosis (years)	
18-34	275 (53.40)
35+	240 (46.60)
Sex	
Male	298 (58.09)
Female	215 (41.91)
Episode type	
New	479 (93.19)
Re-treatment	35 (6.81)
TB site, smear and culture status	
Pulmonary smear or culture positive	246 (47.77)
Pulmonary smear and culture negative	131 (25.44)
Non-pulmonary	138 (26.80)
Patient burden at treatment clinic	
Low burden (n=13)	274 (53.31)
High burden (n=5)	240 (46.69)

Table 3.2 shows the summary of the TB treatment duration and outcomes. The median length of treatment was 6.39 months (IQR 5.67-7.44). The median time to LTFU was 3.67 months (IQR 1.54-6.33), which would be during the continuation phase. The majority of patients (82.33%) changed treatment phase at some point during treatment. The median time to change of treatment phase was 2.36 months (IQR 2.03-3.02).

The majority of the participants were on TB treatment for six to nine months. LTFU was highest in the first two months of treatment (26.97%), and lowest four to six months into treatment (16.85%). Change of treatment phase was highest two to four months after the start of treatment (74.53%).

Four hundred participants (77.67%) had a successful treatment outcome. Of these, 297 (56.67%) were cured, and 103 (20%) completed TB treatment (results not shown). Two participants (0.39%) experienced treatment failure and 24 participants (4.66%) died during treatment. Eighty-nine participants (17.28%) were lost to follow-up. Of these, 29 participants had default as their treatment outcome and 60 participants had a missing treatment outcome.

Table 3.2: Description of TB treatment duration and outcomes

Variable	**Median (IQR)**
Length of treatment (months)	6.39 (5.67-7.44)
Time to LTFU (months)	3.67 (1.54-6.33)
Time to change of treatment phase (months)	2.36 (2.03-3.02)
Variable	**N (%)**
Change of treatment phase	
No	47 (9.13)
Yes	424 (82.33)
Unknown/missing	44 (8.54)
TB treatment outcome	
Success	400 (77.67)
LTFU	89 (17.28)
Died	24 (4.66)
Treatment failure	2 (0.39)
Loss to follow-up	
No LTFU	426 (82.72)
LTFU	89 (17.28)
Length of treatment (months)	
Less than 6	149 (28.93)
6-9	283 (54.95)
9-12	39 (7.57)
Unknown/missing	44 (8.54)
Time to LTFU (months)	
Less than 2	24 (26.97)
2-4	17 (19.10)
4-6	15 (16.85)
6-12	23 (25.84)
Unknown/missing	10 (11.24)
Time to change of treatment phase (months)	
Less than 2	56 (13.21)
2-4	316 (74.53)
4-6	17 (4.01)
6-12	3 (0.71)
Unknown/missing	32 (7.55)

Figure 3.1 shows the distribution of treatment outcome by treatment clinic. LTFU, death and treatment failure were categorised as poor treatment outcomes. At all clinics, the majority of participants had a successful treatment outcome. The most common poor outcome was LTFU, which was observed at all but two clinics. Seventy-seven percent of the poor outcomes were LTFU.

Clinics J, A and R had success rates greater than 90%. Clinics Q, H and B had the lowest TB treatment success rates of 63%, 64% and 65% respectively. No poor treatment outcomes were observed at Clinics K and O. Clinics Q, H and B had the highest proportions of poor outcomes (38%, 36% and 35% respectively). At Clinic Q, the only poor outcome recorded was LTFU. Treatment failure was recorded at Clinics G and M.

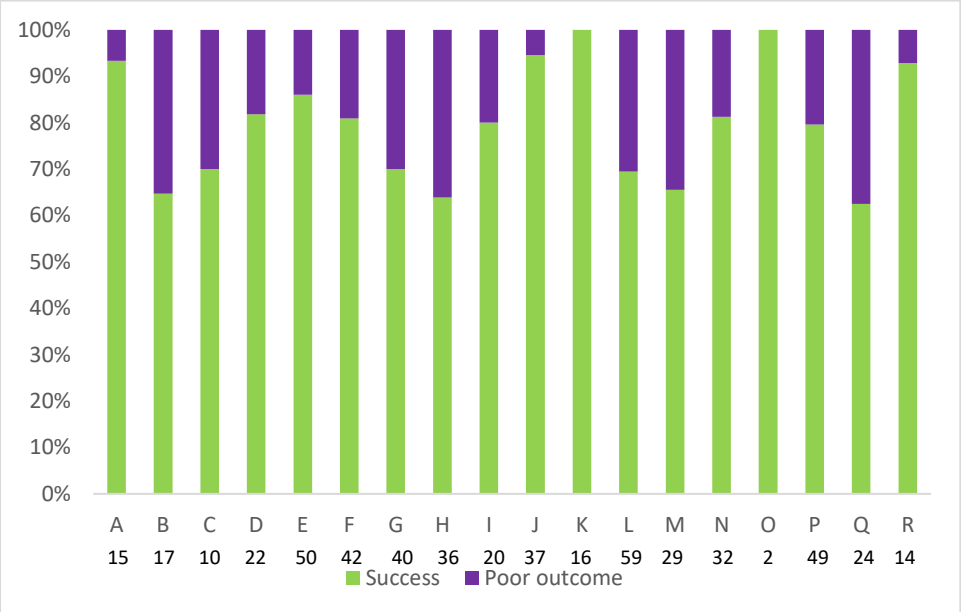

Figure 3.1: TB treatment outcome by treatment clinic. Poor outcomes consisted of LTFU (17.12%), died (4.67%) and treatment failure (0.39%). The total number of participants at each treatment clinic is shown. One participant was excluded from this analysis as information on the treatment clinic attended was not available.

Figure 3.2 shows treatment outcome by the patient burden at the treatment clinics. Almost equal proportions of treatment success and poor outcomes were observed in low and high patient burden treatment clinics. In the clinics with a low patient burden, 22% of participants had a poor treatment outcome while 23% had a poor treatment outcome in the high patient burden clinics.

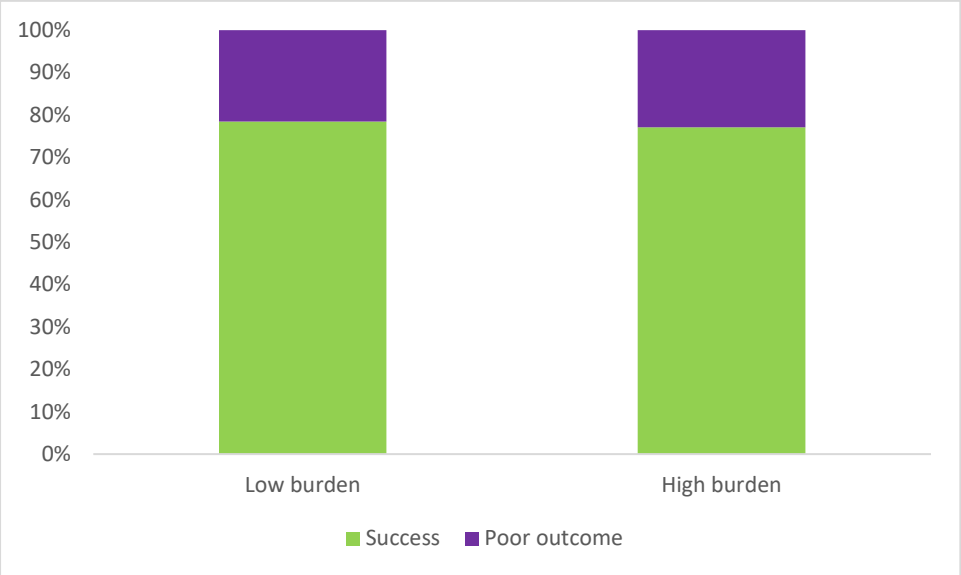

Figure 3.2: TB treatment outcome by patient burden at treatment clinic. Poor outcomes consisted of LTFU (17.12%), died (4.67%) and treatment failure (0.39%). One participant was excluded from this analysis as information on the treatment clinic was not available. No statistically significant difference in levels of poor outcomes was observed between low and high patient burden clinics.

3.2 Burden of LTFU among study participants

Table 3.3 shows the results of the comparison of demographic and clinical characteristics among those who were lost to follow-up and those who were not lost to follow-up. The p-value shown is for the categorical variables.

An overwhelmingly significant difference in the median length of treatment was found between participants who were lost to follow-up and participants who were not lost to follow-up. Most LTFU occurred in the first six months of treatment, and as expected, these participants had a lower median duration of treatment than participants who were not lost to follow-up. Participants who were lost to follow-up may not have been on TB treatment long enough to change treatment phase, resulting in a significant difference in LTFU being observed among participants who changed treatment phase and those who did not change treatment phase.

The difference in the time to change of treatment phase between the two groups was not statistically significant. With the exception of participants who changed treatment phase between two and twelve months after treatment commencement, participants who were lost to follow-up had a lower median time to change of treatment phase compared to participants who were not lost to follow-up. No participants were lost to follow-up four to six months after treatment began. Those who were lost to follow-up had the same median age as those who were not lost to follow-up for both age categories. No significant differences in age, sex, episode type, patient burden at treatment site and TB site, smear and culture status were observed among those who were lost to follow-up and those who were not lost to follow-up.

Table 3.3: Burden of LTFU among HIV-uninfected TB patients by selected demographic and clinical characteristics

Variable	No LTFU [n (%)]	LTFU [n (%)]	p-value
Age at TB diagnosis (years)			0.201
18-34	222 (80.73)	53 (19.27)	
Median (IQR)	*26 (23-30)*	*26 (24-29)*	
35+	204 (85.00)	36 (15.00)	
Median (IQR)	*48 (42-55)*	*48 (40-57)*	
Length of treatment (months)			< 0.001
Less than 6	93 (62.42)	56 (37.58)	
Median (IQR)	*5.34 (3.90-5.77)*	*2.31 (0.97-4.11)*	
6-9	265 (93.64)	18 (6.36)	
Median (IQR)	*6.69 (6.26-7.61)*	*7.13 (6.72-7.38)*	
9-12	34 (87.18)	5 (12.82)	
Median (IQR)	*9.55 (9.18-10.10)*	*9.80 (9.70-10.30)*	
Unknown/missing	34 (77.27)	10 (22.73)	
Time to change of treatment phase (months)			0.375
Less than 2	51 (91.07)	5 (8.93)	
Median (IQR)	*1.84 (1.64-1.93)*	*1.77 (1.64-1.97)*	
2-4	287 (90.82)	29 (9.18)	
Median (IQR)	*2.46 (2.10-2.98)*	*2.98 (2.30-3.18)*	
4-6	17 (100.00)	0 (0.00)	
Median (IQR)	*4.56 (4.16-4.89)*	-	
6-12	2 (66.67)	1 (33.33)	
Median (IQR)	*6.95 (6.26-7.64)*	*7.08 (7.08-7.08)*	
Unknown/missing	30 (93.75)	2 (6.25)	
Sex			0.759
Male	245 (82.21)	53 (17.79)	
Female	179 (83.26)	36 (16.74)	
Episode type			0.369
New	398 (83.09)	81 (16.91)	
Re-treatment	27 (77.14)	8 (22.86)	
TB site, smear and culture status*			0.605
A	202 (82.11)	44 (17.89)	
B	112 (85.50)	19 (14.50)	
C	112 (81.16)	26 (18.84)	
Change of treatment phase			<0.001
No	22 (46.81)	25 (53.19)	
Yes	387 (91.27)	37 (8.73)	
Unknown/missing	17 (38.64)	27 (61.36)	
Patient burden at treatment clinic			0.624
Low burden	225 (82.12)	49 (17.88)	
High burden	201 (83.75)	39 (16.25)	

* **A**: Pulmonary smear or culture positive; **B**: Pulmonary smear and culture negative; **C**: Non-pulmonary

3.3 Factors associated with LTFU

Table 3.4 shows the results of the univariate logistic regression analysis used to determine the factors associated with LTFU during TB treatment in HIV-uninfected TB patients. No factor was found to be significantly associated with LTFU during TB treatment. Participants aged 35 years and above had a 26% lower risk of LTFU than participants aged 18-34 years. Female participants were 7% less likely to be lost to follow-up compared to men. Participants with smear and culture negative pulmonary TB had 22% lower risk of LTFU compared to participants with smear or culture positive pulmonary TB. Participants with non-pulmonary TB had a 7% higher risk of LTFU than participants with smear or culture positive pulmonary TB. Participants who received TB treatment at clinics with a high patient burden had an 11% lower risk of LTFU than participants treated a clinic with a low patient burden.

Table 3.4: Results of the univariate logistic regression to determine factors associated with LTFU

Factor	Odds ratio	95% CI	p-value
Age at TB diagnosis			
18-34	1 (base)		
35+	0.74	0.46-1.18	0.202
Sex			
Male	1 (base)		
Female	0.93	0.58-1.48	0.759
Episode type			
New	1 (base)		
Re-treatment	1.46	0.64-3.32	0.372
TB site, smear and culture status *			
A	1 (base)		
B	0.78	0.43-1.40	0.403
C	1.07	0.62-1.82	0.816
Patient burden at treatment clinic			
Low	1 (base)		
High	0.89	0.56-1.41	0.624

* **A**: Pulmonary smear or culture positive; **B**: Pulmonary smear and culture negative; **C**: Non-pulmonary

Table 3.5 shows the results of the multivariate logistic regression analysis. Age at TB diagnosis and sex were the variables included in the multivariate analysis. No statistically significant association between age at TB diagnosis, sex and LTFU was found. Participants aged 35 years and above were 27% less likely to be lost to follow-up than participants aged 18-34 years. Female participants had a lower risk of LTFU (OR 0.89, 95% CI 0.55-1.42; p = 0.620) than male participants. No confounding or interaction between the variables was observed. Goodness of fit of the model was observed (p = 0.472).

Table 3.5: Results of multivariate logistic regression to determine the factors associated with LTFU (N = 513)

Factor	Adjusted odds ratio	95% CI	p-value
Age at TB diagnosis			
18-34	1 (base)		
35+	0.73	0.45-1.16	0.183
Sex			
Male	1 (base)		
Female	0.89	0.55-1.42	0.620

3.4 Survival analysis

Data from 469 participants were used in the survival analysis due to missing or incorrect dates. Seventy-five participants had the outcome of interest (LTFU) during the 12-month follow-up. The incidence rate of LTFU among the study participants was 2.51 (95% CI 2.00-3.15) per 100 person-months. The total person-time of follow-up was 2 985 months.

Figure 3.3 shows the Kaplan-Meier failure curve. The graph shows the probability of LTFU over 12 months of follow-up. The probability of LTFU was found to increase with increasing time. During the first six months of follow up the increase was at a constant rate. The probability of LTFU was 4% after two months and 12% at six months.

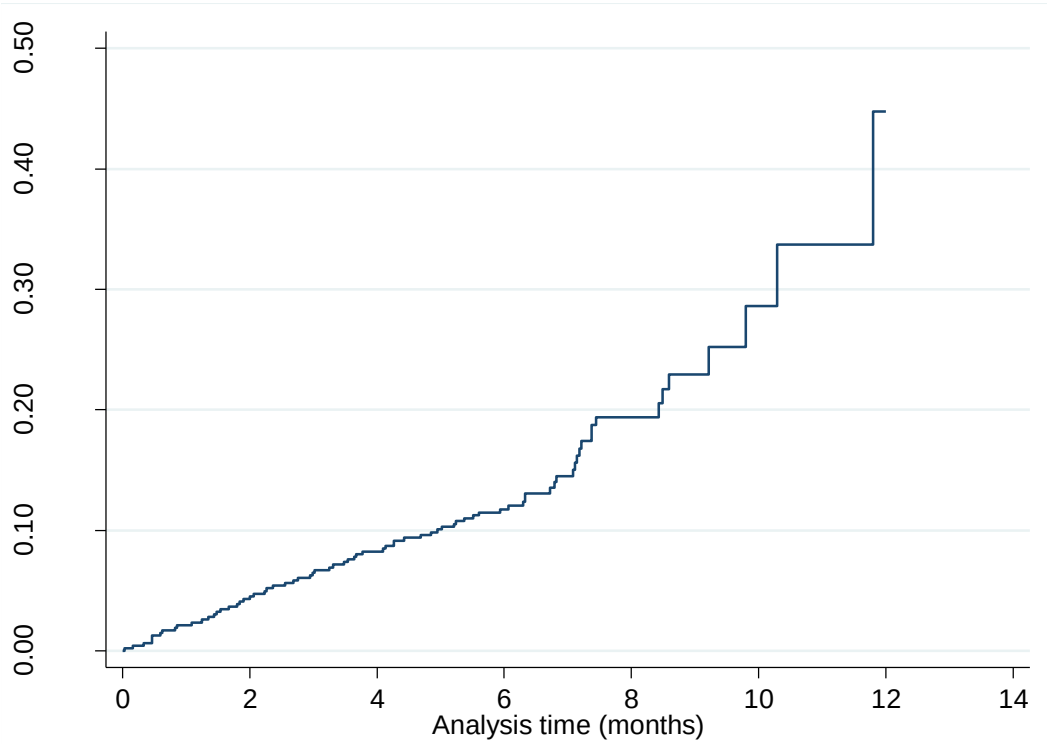

Figure 3.3: Probability of LTFU over 12 months of follow-up

Table 3.6 shows the results of the survival analysis. No statistically significant differences in survival functions between the different categories were observed for all of the tested variables. Participants aged 18-34 years had a higher incidence rate of LTFU (2.79 per 100 person-months; 95% CI: 2.08-3.75) than participants aged 35 years and above (2.20 per 100 person-months; 95% CI: 1.55-3.13). Male participants had a slightly higher incidence rate of LTFU (2.55 per 100 person-months; 95% CI: 1.90-3.41) than female participants (2.49 per 100 person-months; 95% CI: 1.74-3.56).

Participants with a new TB episode had a slightly lower incidence rate of LTFU than participants who had a retreatment episode of TB. The incidence rate of LTFU among re-retreatment TB cases was 2.90 per 100 person-months (95% CI: 1.30-6.45). Participants with smear or culture positive pulmonary TB had the highest rate of LTFU (2.76 per 100 person-

months; 95% CI: 2.02-3.78). The lowest rate was seen among participants with smear and culture negative pulmonary TB (1.92 per 100 person-months; 95% CI: 1.16-3.18). Participants who received treatment at clinics with a low patient burden had a higher incidence rate of LTFU (2.57 per 100 person-months; 95% CI: 1.90-3.48) than participants who were treated at clinics with a high patient burden (2.46 per 100 person-months; 95% CI: 1.75-3.46).

Table 3.6: Survival analysis: Time to LTFU among HIV-uninfected TB patients

Factor	Losses to follow-up (n)	Person-months of follow-up	Rate (per 100 person-months)	95% CI	p-value
Age at TB diagnosis					0.227
18-34	44	1 576	2.79	2.08-3.75	
35+	31	1 408	2.20	1.55-3.13	
Gender					0.974
Male	45	1 765	2.55	1.90-3.41	
Female	30	1 205	2.49	1.74-3.56	
Episode type					0.789
New	69	2 778	2.48	1.96-3.14	
Re-treatment	6	207	2.90	1.30-6.45	
TB site, smear and culture status *					0.441
A	39	1 413	2.76	2.02-3.78	
B	15	782	1.92	1.16-3.18	
C	21	790	2.66	1.73-4.08	
Patient burden at treatment clinic					0.883
Low	42	1 633	2.57	1.90-3.48	
High	33	1 340	2.46	1.75-3.46	

* **A**: Pulmonary smear or culture positive; **B**: Pulmonary smear and culture negative; **C**: Non-pulmonary

3.5 Cox proportional hazards regression

Table 3.7 shows the results of the univariate Cox proportional hazards regression analysis. None of the variables investigated had a significant association with LTFU. The probability of LTFU was lower in participants aged 35 years and older (HR 0.75; 95% CI: 0.47-1.20; p-value: 0.229) than in participants aged 18-34 years. The probability of LTFU was only one percent

lower in female participants than male participants. Participants with a re-treatment TB episode had a 12% higher probability of LTFU than in participants with a new TB episode. Participants with smear and culture negative pulmonary TB had the lowest probability of LTFU (HR: 0.68; 95% CI: 0.38-1.24; p-value: 0.208). The probability of LTFU in participants who received treatment at clinics with a high patient burden was 3% lower than in participants treated at clinics with a low patient burden.

Table 3.7: Results of the univariate Cox proportional hazards regression analysis

Factor	**Hazard ratio**	**95% CI**	**p-value**
Age at TB diagnosis			
18-34	1 (base)		
35+	0.75	0.47-1.20	0.229
Sex			
Male	1 (base)		
Female	0.99	0.62-1.58	0.974
Episode type			
New	1 (base)		
Re-treatment	1.12	0.49-2.59	0.789
TB site, smear and culture status *			
A	1 (base)		
B	0.68	0.38-1.24	0.208
C	0.85	0.50-1.46	0.564
Patient burden at treatment clinic			
Low	1 (base)		
High	0.97	0.61-1.53	0.883

* **A**: Pulmonary smear or culture positive; **B**: Pulmonary smear and culture negative; **C**: Non-pulmonary

Table 3.8 shows the results of the multivariate Cox proportional hazards regression analysis. Age and sex were included in the adjusted analysis. Participants aged 35 years and above had a 25% (95% CI: 0.47-1.19; p = 0.225) lower risk of LTFU than participants aged 18-34 years and below. The risk of LTFU among female participants was slightly lower than that among

male participants (HR 0.95; 95% CI: 0.64-1.53; p = 0.976). No confounding or interaction was observed. The proportional hazards assumption of the model was satisfied (p = 0.212).

Table 3.8: Results of the multivariate Cox proportional hazards regression analysis to find factors associated with LTFU (N=467)

Factor	Hazard ratio	95% CI	p-value
Age at TB diagnosis			
18-34	1 (base)		
35+	0.75	0.47-1.19	0.225
Sex			
Male	1 (base)		
Female	0.95	0.60-1.52	0.846

3.6 Sensitivity analyses

The results of the sensitivity analyses for the regression analyses are presented in Tables 3.9 - 3.11.

Analysis 1

For the logistic regression, the results (presented in Table 3.9) showed that excluding the possible data errors does not change the results. Possible data errors were excluded by censoring analysis at 8 months. The estimated odds ratios, 95% CIs and p-values were exactly the same in the 8 and 12-month analysis.

Analysis 2

The results of sensitivity analysis 2 are shown in Table 3.10. For the Cox proportional hazards regression, 68 and 75 participants experienced LTFU for the 8-month and 12-month follow-up periods respectively. The results were similar but not identical for age at TB diagnosis. The hazard ratios were identical, but the 95% CIs and the p-values were different. In the uncensored

analysis, the female participants had a 5% lower risk of LTFU compared to the male participants, while in the censored analysis, the female participants had a 5% higher risk of LTFU compared to the male participants.

Table 3.9: Results of the sensitivity analysis for the multivariate logistic regression. Data were either not censored (12 months follow-up) or were censored at 8 months of follow-up.

Factor	Adjusted odds ratio (not censored)	Adjusted odds ratio (censored)	95% CI (not censored)	95% CI (censored)	p-value (not censored)	p-value (censored)
Age at TB diagnosis						
18-34	1 (base)					
35+	0.73	0.73	0.45-1.16	0.45-1.16	0.183	0.183
Sex						
Male	1 (base)					
Female	0.89	0.89	0.55-1.42	0.55-1.42	0.620	0.620

Table 3.10: Results of the sensitivity analysis for the multivariate Cox proportional hazards regression. Data were either not censored (12 months follow-up) or were censored at 8 months of follow-up.

Factor	Hazard ratio (not censored)	Hazard ratio (censored)	95% CI (not censored)	95% CI (censored)	p-value (not censored)	p-value (censored)
Age at TB diagnosis						
18-34	1 (base)					
35+	0.75	0.75	0.47-1.19	0.46-1.22	0.225	0.245
Sex						
Male	1 (base)					
Female	0.95	1.05	0.60-1.52	0.65-1.71	0.846	0.834

Analysis 3

Table 3.11 shows the results of the sensitivity analysis conducted around the definition of LTFU. In both analyses, female participants and participants over the age of 35 years had a lower risk of LTFU than male participants and participants ages 18-34 years respectively. When only participants who were assigned the outcome default in the primary study were considered lost to follow-up, sex was significantly associated with LTFU. Female participants had a 66% lower risk of LTFU compared to male participants. Participants with pulmonary smear and culture negative had a statistically significant lower risk of LTFU compared to participants with pulmonary smear or culture positive TB. However, goodness of fit of the model was not observed ($p = 0.016$).

Table 3.11: Results of the sensitivity analysis around the definition of LTFU. The results of multivariate logistic regression conducted when participants whose treatment outcomes in the primary study were default and missing were considered lost to follow-up were compared to multivariate logistic regression conducted when only those whose outcome in the primary was default. (N = 513)

Factor	**Adjusted odds ratio (default + missing)**	**Adjusted odds ratio (defaulted only)**	**95% CI (default + missing)**	**95% CI (defaulted only)**	**p-value (default + missing)**	**p-value (defaulted only)**
Age at TB diagnosis						
18-34	1 (base)					
35+	0.73	0.81	0.45-1.16	0.38-1.75	0.183	0.594
Sex						
Male	1 (base)					
Female	0.89	0.34	0.55-1.42	0.13-0.85	0.620	0.022
TB site, smear and culture status*						
A	1 (base)					
B	-	0.28	-	0.08-0.98	-	0.047
C	-	0.69	-	0.28-1.69	-	0.415

* **A**: Pulmonary smear or culture positive; **B**: Pulmonary smear and culture negative; **C**: Non-pulmonary

CHAPTER 4: DISCUSSION

The purpose of the discussion is to discuss the results obtained in this study and compare them to previously published results in the literature. The limitations of the study, conclusions and recommendations will also be presented be in this chapter.

The aim of this study was to determine the demographic and clinical factors associated with LTFU in HIV-uninfected TB patients who registered for TB treatment in Ekurhuleni North sub-district from 1st January 2011 to 30th June 2012.

Summary of findings

The results of this study show that LTFU is common among HIV-uninfected TB patients in Ekurhuleni North sub-district. Seventeen percent of the study participants were lost to follow-up during TB treatment using the broader definition of default and no treatment outcome as LTFU. LTFU was found to occur throughout TB treatment. None of the factors investigated were significantly associated with LTFU. When using the definition of default only as LTFU (for the sensitivity analysis), the rate of LTFU was 5.63% and was associated with participant's sex. Female participants had a 66% lower risk of LTFU than male participants.

Burden of LTFU

The rate of LTFU in this study was 17%, which was higher than the WHO's acceptable rate of LTFU during TB treatment of 5% (Belchior et al., 2016). The rate of LTFU in Ekurhuleni (for HIV-infected and uninfected patients) was 4.6% among patients with new, smear positive pulmonary TB in 2014 (Massyn et al., 2016). Our study involved HIV-uninfected patients with smear positive and negative pulmonary TB, EPTB and new and retreatment TB cases. As the participants in this study had a range of TB infection types, the observed rates of LTFU would

be higher than those previously published by Massyn *et al*. (2016). Only 18 of 32 treatment clinics in Ekurhuleni North were selected for the study. Selecting these 18 clinics may have resulted in the selection of clinics that have higher rates of LTFU. Furthermore, the use of a more inclusive definition of LTFU may have contributed to the high rate of LTFU observed, as more participants experienced LTFU when we used the expanded definition of LTFU.

The high rate of LTFU observed was unexpected as HIV-infected TB patients have a higher risk of LTFU than HIV-uninfected TB patients (Ifebunandu and Ukwaja, 2012, Muture et al., 2011) and this study did not involve any HIV-infected participants. Pepper *et al*. (2012) proposed that HIV-infected TB patients may have improved follow-up as regular clinic attendance is required on ART to avoid life-threatening illness. In stark contrast to the ART programme, the preparation of patients to receive TB treatment is minimal and is not standardised (Dong et al., 2007). HIV-uninfected TB patients may, therefore, have a lower understanding of the importance of remaining on TB treatment.

The three districts with the highest incidence rates of TB in South Africa in 2015 had more than 900 incident cases per 100 000 population, and had LTFU rates of 7.3-8.8% (Massyn et al., 2016). The rate of LTFU observed in this study was most similar to the rate of LTFU in ZF Mgcawu district in Northern Cape Province (16.5%), which had 856 incident cases of TB per 100 000 population (Massyn et al., 2016). When only default was used as LTFU in the sensitivity analysis, a lower rate of LTFU than that in the three districts was observed. This rate of LTFU (5.63%) can be considered to be the minimum rate of LTFU for this study. The maximum rate of LTFU, 17%, was much higher than the minimum rate. The inability to confirm the treatment outcome of the 60 participants classified as LTFU due to a missing treatment outcome and possible differences in the capacities of districts to trace patients may

explain the differences in LTFU rates. The districts with high incidence rates of TB may invest more money into tracing TB patients, which may explain the lower rates of LTFU observed.

The rates of LTFU observed in this study were much higher than those found in other countries. The national average LTFU rate in Benin is 1% (Ade et al., 2016). Benin has achieved a 1% LTFU rate through interventions such as nutritional support and the use of a special Basic Management Unit that traces patients that miss DOTS sessions and other scheduled appointments (Ade et al., 2016). LTFU rates in Kenya ranged from 5.5% in a study using national data (Sitienei et al., 2015) to 13.3% in an urban informal settlement (Kizito et al., 2011). Ten percent LTFU was observed in a study conducted in Southern Mozambique (García-Basteiro et al., 2016). LTFU rates were 14% in Kampala, Uganda (Sendagire et al., 2012) and in Brazil (Garrido et al., 2012). In Europe, a study in Russia observed a 4.6% rate of LTFU (Jakubowiak et al., 2009) and one in Belarus a rate of 13% (Khaliaukin et al., 2014). Differences in TB disease burden, health policy and economic factors may account for the differences in the rates of LTFU. In countries with a low burden of TB disease, it may be easier to trace patients that have missed TB treatment appointments, while health policies may inform how countries deal with LTFU. Poor or non-existent policies are likely to result in an increase in rates of LTFU. Economic factors may increase the burden of LTFU if TB patients are unable to afford to miss work or buy nutritional supplements.

More study participants were aged 18-34 years than 35 years and above. The highest number of TB notifications are among 20-40 year olds (Wood et al., 2010). Younger people may be more susceptible to be TB due to behaviour patterns, migration due to work and a low socioeconomic status that influences exposure to poor housing conditions. No differences in

median age were observed among those who were lost to follow-up and those who were not lost to follow-up in the two age categories in this study.

Although a higher proportion of participants aged 18-34 were lost to follow-up compared to those aged 35 years and older, the difference was not statistically significant. A previous study in Ghana found that LTFU rates were significantly higher in younger participants than older participants (Dodor, 2004). Younger participants may have higher rates of LTFU as following migration for work they may lose the support systems they had prior to migrating, which increases their risk of LTFU (Kulkarni et al., 2013). Peer pressure is likely to be a more significant contributing factor to LTFU in younger people than older people as group norms affect treatment adherence (Martin et al., 2005). Younger TB patients may feel that to fit in and be accepted by their peers they cannot continue TB treatment.

Although the majority of those lost to follow-up in this study were male, no significant difference in LTFU was found between male and female participants. A previous study found that men were more likely to experience LTFU than women, probably due to men shunning healthcare services more than women (Belchior et al., 2016). The stigma associated with TB and societal expectations may prevent men from seeking or remaining in care as they may not want to be perceived as weak or ill. In families where the male TB patient is the primary breadwinner, seeking care may mean a loss of income for the family. In Kenya, many male TB patients who experienced LTFU worked as casual workers so they did not have the benefit of sick leave (Kizito et al., 2011). The same may be true in Ekurhuleni North, leading men to opt to abandon treatment in order to provide for their families. Expenses associated with care can increase poverty and increase the risk of poor outcomes (Saunders and Evans, 2016). In Ekurhuleni, men are breadwinners in 69% of households (Statistics South Africa, 2016). A

study in Pakistan found that patients who stopped treatment early felt guilty about the negative effects that their diagnosis and treatment would have on their families (Chida et al., 2015).

Participants with a retreatment TB episode had a higher rate of LTFU than participants with a new TB episode, but the difference was not statistically significant. Previous studies involving HIV-infected and uninfected TB patients found that LTFU was higher in retreatment TB cases compared to new cases TB cases (Kigozi et al., 2017, Pardeshi, 2010). In the study by Kigozi *et al*. (2017), participants with retreatment TB were twice more likely to be lost to follow-up than participants with a new TB episode. Maximum LTFU occurred earlier in new cases compared to retreatment cases (Pardeshi, 2010), suggesting that the retreatment TB patients had a better understanding of the importance of remaining on TB treatment. Similar results were observed in this study, with maximum LTFU occurring in the first two months of treatment for new TB cases and two to five months into treatment for retreatment TB cases (results not shown).

TB patients with retreatment TB may do their best to remain on TB treatment for a longer period of time as they have had at least two TB treatment counselling sessions (one at the beginning of each treatment episode) which may increase their understanding of treatment. A desire to obtain a good treatment outcome in their second round of treatment may also motivate them to remain on treatment longer than TB patients with a new TB episode. However, if the circumstances that led to the participants with retreatment TB leaving treatment prematurely initially have not changed, they are likely to fail to adhere to treatment again.

It was expected that participants with EPTB would have higher rates of LTFU than participants with pulmonary TB. However, no significant difference in LTFU was observed. Although

treatment for drug sensitive pulmonary TB normally lasts six to eight months, participants with EPTB may be on treatment for extended periods of time. Some treatment experts prefer patients to remain on treatment for at least 12 months or until there is pathological or radiological evidence of disease regression (Lee, 2015).

For some participants that were on TB treatment for more than one year, it is possible that the participants were lost to follow-up during treatment, but later returned and that this was not indicated in the original records. The continuation phase in TB treatment is normally 4 months long, but TB patients who have cavitary pulmonary disease, a positive sputum test at 2 months or are not treated with pyrazinamide during the intensive phase will have a 7-month long continuation phase (CDC, 2016). The data used in this study did not indicate whether or not this was the case for the participants who had extended treatment periods.

The patient burden at treatment clinic did not affect rates of LTFU, as the rates of LTFU were similar between low and high patient burden clinics. This was surprising as a study conducted in South Africa on HIV found that treatment facilities with large numbers of patients can provide high-quality care as they would have more staff than facilities with fewer patients and the types of staff would be different (MacLeod et al., 2016). An example is that the large facilities are more likely to have specialist services. The clinics with high patient burdens may be prioritised when health planning occurs, receiving more human and financial resource allocations for patient care. Inadequate numbers of staff and resources can have a negative impact on the retention of patients in care. LTFU in South Africa may be driven by the history of neglect, poor patient management (likely due to constraints on healthcare workers) and fragmented health services (Weyer, 2007).

Timing of LTFU

LTFU was found to occur throughout TB treatment. Although the highest proportion of LTFU occurred in the first two months of TB treatment, LTFU was occurring at all times during the follow-up period with a steady increase in risk over the first six months of follow-up. LTFU will occur throughout treatment as at each point in the treatment period there are different factors that influence LTFU. During the intensive phase of treatment, being older than 45 years, the inconvenience of the treatment programme, work related problems and being symptom free can increase the risk of LTFU (Chandrasekaran et al., 2005). In the continuation phase of treatment, feeling better or worse can influence a patient to abandon treatment, as well as follow-up tests not being conducted (Akessa et al., 2015). TB patients may think that improved symptoms mean that they have been cured of TB (Dodor, 2004). Patients may also be demotivated by the length and complexity of treatment (Kruk et al., 2008, Martin et al., 2005).

Time to LTFU varies in different countries and settings, with studies reporting median times to LTFU ranging from 1.6 months to 4.1 months (Hoa et al., 2012, Ifebunandu and Ukwaja, 2012, Jenkins et al., 2013). The differences in median times to LTFU can be attributed to a variation in the factors influencing LTFU in different settings. As an example, residing in an urban residence in Morocco is significantly associated with LTFU while in Nigeria, a rural residence increases the risk of LTFU (Tola et al., 2015). Differences in TB treatment protocols may also influence this difference. In Ghana, different facilities are used in the intensive and continuation phases of treatment (Dodor, 2004). The change in treatment facility may cause confusion or be inconvenient for the patient. The change may also make it difficult for healthcare workers to trace patients that have stopped receiving treatment. In South Africa, the same treatment facility is used for all stages of treatment unless the patient transfers out.

None of the variables investigated had a statistically significant effect on time to LTFU. A previous study found that TB patients who received treatment at public facilities, male TB patients and retreatment after LTFU TB patients had significantly shorter times to LTFU (Masini et al., 2016). Factors that were not investigated in this study may have had an effect on the time to LTFU in Ekurhuleni North sub-district.

There was collinearity between the main outcome, LTFU, and length of treatment and change of treatment phase. Participants who are lost to follow-up during TB treatment are expected to have shorter treatment times, and so are less likely to change treatment phase. The two variables, length of treatment and change of treatment phase, are also outcomes of TB treatment, and so cannot be treated as factors in regression analysis. Forty-two percent of the participants who were lost to follow-up changed treatment phase during TB treatment.

Change of treatment phase was not a confounder in this study. A confounder is a risk factor that is associated with the outcome of interest as well as the exposure but is not a result of the exposure. TB patients begin treatment, change treatment phase after 2 months, then continue treatment until its completion. As a change of treatment phase is on the pathway from start of treatment to treatment completion, it cannot occur without treatment initiation, nor can TB treatment be completed without a change of treatment phase. As a result, change of treatment phase is not a confounder. In research studies, confounders can be dealt with by using matching in the design phase or by using stratification or adjustment in the data analysis phase. As secondary data analysis was used in this study, the only options for dealing with any confounders were stratification or adjusting for the confounder in regression analysis. Given that the change of phase was not a confounder, adjusting for it in regression analysis was not necessary.

Factors associated with LTFU

No factors in this study were found to be significantly associated with LTFU. None of the factors had a p-value of less than 0.2 in univariate regression analysis, so only age and sex were included in multivariate logistic regression *a priori*. Cox proportional hazards regression analysis gave similar results to logistic regression analysis.

In some previous studies, the factors investigated in this study were found to influence LTFU. Gafar *et al*. (2014) found that age was significantly associated with LTFU. Men had a higher risk of LTFU than women in Argentina (Herrero et al., 2015). Episode type was significantly associated with LTFU, with patients with a retreatment episode of TB having a higher risk of LTFU than those with a new TB episode (Cherkaoui et al., 2014). Patients with EPTB had a higher risk of LTFU than participants with pulmonary TB (Hoa et al., 2012), and the enrolment of a large number of patients (more than one hundred) in a TB treatment programme was found to promote LTFU (Moyo et al., 2015).

On the other hand, similar results to the ones obtained in this study were found in some studies. Akessa *et al*. (2015) did not observe a significant association between age, sex and LTFU. Episode type did not affect LTFU in a study by Sanchez-Padilla *et al*. (2014), nor did type of TB in another (Nglazi et al., 2015).

The limited number of variables and the missing data may have contributed to the failure to find factors associated with LTFU in this study. It is possible that the factors that are significantly associated with LTFU in Ekurhuleni North sub-district among HIV-uninfected TB patients were not investigated in this study. Adherence to TB treatment is a complex and dynamic phenomenon as many factors affect treatment taking behaviour (Ershova et al., 2014).

It is important to establish what factors lead to LTFU in a particular setting in order to have effective interventions.

Methodological issues

In both logistic regression and Cox proportional hazards regression, none of the factors investigated were significantly associated with LTFU. The trends observed with logistic regression analysis, for example, women having a lower risk of LTFU than men, were observed with Cox proportional hazards regression. There was however one exception. In univariate logistic regression analysis, participants with non-pulmonary TB had a higher risk of LTFU compared to participants with pulmonary smear or culture positive TB. However, in univariate Cox proportional hazards regression, participants with non-pulmonary TB had a lower risk of LTFU.

A possible reason for the differences observed with logistic and Cox proportional hazards regression is that the two regression methods are different. Logistic regression models are fully parametric while Cox proportional hazards regression models are semiparametric. Logistic regression analysis will give a response toward the beginning of follow-up equal weight with a response towards the end of analysis (Moriguchi et al., 1993). The Cox model, on the other hand, will incorporate the covariates measured on each individual and will use the response time in analysis (Moriguchi et al., 1993). The assumptions for the two models are different. Logistic regression assumes independent observations, while Cox proportional hazards regression assumes that censoring is independent of the time to event, proportional hazards and independent observations.

Sensitivity analysis was conducted for the multivariate logistic regression and Cox proportional hazards regression. Sensitivity analysis is used to estimate the effect bias could have on an estimate by simulating different scenarios. It has been described as "the last line of defence against biases after every effort has been made to eliminate, control or reduce them in study design, data collection and data analysis" (Schneeweiss, 2006). It is important to test the assumptions used in the design of a study as these assumptions may influence the results if they are not met (Thabane et al., 2013). Consistency in the results obtained strengthens the credibility of the findings (Thabane et al., 2013).

The logistic regression results are consistent and can, therefore, be considered credible. The results of the Cox proportional hazards regression sensitivity analysis are different for the participant's sex. Female participants had a 5% lower risk of LTFU compared to male participants in the uncensored analysis and a 5% higher risk of LTFU in the censored analysis. The difference observed may be due to the fact that in the censored Cox proportional hazards regression analysis, only 68 participants experienced LTFU, compared to 75 in the uncensored analysis.

The sensitivity analysis conducted around the definition of LTFU gave different results to the main analysis. Although sex was significantly associated with LTFU, goodness of fit of the model was not observed. This result means that the model gives a poor fit of the data. The inability of the model to accurately predict LTFU may be due to the large number of missing outcomes. The results obtained in the two analyses are not consistent with one another and emphasise the need for complete and accurate records in TB programmes.

Limitations

Several limitations were identified. One limitation in this study was that LTFU was treated as an event instead of a process. LTFU was assumed to occur on the date of the most recent clinic visit. However, as patients would have collected their treatment on this date, it is possible that the patients only stopped taking their medication a few days or weeks after their most recent clinic visit. Using the next scheduled clinic visit date as the date of LTFU would have been more accurate but these data were not collected.

No information was available on what the clinics did to trace the patients that had been lost to follow-up. It is possible that the patients had transferred to another clinic or had died. Knowledge of this is important to evaluate TB treatment programmes and plan effectively. This information will also help researchers to accurately determine the rate of LTFU as well as the factors that contribute to LTFU.

As this study involved secondary data analysis, the study question asked in this study was different from the question that was asked in the primary study. As a result, the variables collected in the primary study were different from the variables required in this study. This study had a limited number of variables, so information on socioeconomic status, residence type, comorbidities, treatment clinics and health system factors was not available. As the primary study focused on Ekurhuleni North, no data on other parts of South Africa was available, so the study results may not be generalizable to other parts of South Africa. Data may have been more incomplete for patients whose illness was more advanced due to hospitalization in a different area or transfer.

Another limitation in this study was missing data. Some variables could not be used as there were not enough responses collected. The missing data in some of the variables used may have affected the results. There may also have been errors in data extraction that could not be detected or corrected. Errors in documenting TB treatment may have occurred. It is possible that some of the errors in the treatment dates observed are due to errors at the treatment clinics. Some patients may have been receiving care at the clinics in this study but not actually registered until long after commencing treatment. Some patients may not have been registered at all due to health system factors, so data related to their treatment would not have been available for this study.

Our study was not designed to measure initial LTFU, which is a major problem in South Africa. Initial LTFU is LTFU that occurs before the beginning of treatment (Massyn et al., 2016). Initial LTFU rates in South Africa range from 4.5% to 38%, depending on the location, treatment settings and whether the data is electronically verified or extracted manually from a TB register (Cele et al., 2016).

Conclusions and Recommendations

LTFU is a common phenomenon in HIV-uninfected patients in Ekurhuleni North sub-district and occurs at all times during TB treatment. Age, sex, episode type, patient burden at treatment clinic and TB site, smear and culture status have no statistically significant effect on LTFU among HIV-uninfected TB patients in Ekurhuleni North sub-district.

It is recommended that studies are conducted to determine the factors influencing LTFU during TB treatment in South Africa with a focus on HIV-uninfected TB patients. HIV-uninfected TB patients are a neglected cohort in treatment planning. Increased attention to the needs of this

group is recommended. Educating the public about TB will help to reduce stigma and therefore LTFU. National statistics should also include pre-treatment LTFU to allow for a more accurate picture of LTFU in South Africa. Finally, ensuring adequate financial and human resource support to treatment clinics is also recommended to reduce LTFU and enabling tracing of TB patients in Ekurhuleni North.

REFERENCES

Ade, S., Trébucq, A., Harries, A. D., Ade, G., Agodokpessi, G., Wachinou, P., Affolabi, D. & Anagonou, S. (2016). Follow-up and tracing of tuberculosis patients who fail to attend their scheduled appointments in Cotonou, Benin: a retrospective cohort study. *BMC Health Services Research,* 16(5).

Akessa, G. M., Tadesse, M. & Abebe, G. (2015). Survival Analysis of Loss to Follow-Up Treatment among Tuberculosis Patients at Jimma University Specialized Hospital, Jimma, Southwest Ethiopia. *International Journal of Statistical Mechanics,* 2015.

Arbex, M. A., Varella, M. D. C. L., Siqueira, H. R. D. & Mello, F. a. F. D. (2010). Antituberculosis drugs: drug interactions, adverse effects, and use in special situations - part 1: first-line drugs. *Jornal Brasileiro de Pneumologia,* 36(5)**,** 626-640.

Belayneh, T., Kassu, A., Tigabu, D., Asmare, G., Tilaye, S. & Klinkenberg, E. (2016). Characteristics and Treatment Outcomes of "Transfer-Out" Pulmonary Tuberculosis Patients in Gondar, Ethiopia. *Tuberculosis Research and Treatment,* 2016.

Belchior, A. D. S., Mainbourg, E. M. T., Ferreira-Gonçalves, M. J., Belchior, A. D. S., Mainbourg, E. M. T. & Ferreira-Gonçalves, M. J. (2016). Loss to follow-up in tuberculosis treatment and its relationship with patients' knowledge of the disease and other associated factors. *Revista de Salud Pública,* 18(5)**,** 714-726.

Brust, J. C. M., Gandhi, N. R., Carrara, H., Osburn, G. & Padayatchi, N. (2010). High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000-2003. *The International Journal of Tuberculosis and Lung Disease: The Official Journal of the International Union Against Tuberculosis and Lung Disease,* 14(4)**,** 413-419.

Budgell, E. P., Evans, D., Schnippel, K., Ive, P., Long, L. & Rosen, S. (2016). Outcomes of treatment of drug-susceptible tuberculosis at public sector primary healthcare clinics in Johannesburg, South Africa: A retrospective cohort study. *South African Medical Journal,* 106(10)**,** 1002-1009.

Caminero, J. A., Sotgiu, G., Zumla, A. & Migliori, G. B. (2010). Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. *The Lancet Infectious Diseases,* 10(9)**,** 621-629.

Caylà, J. A., Rodrigo, T., Ruiz-Manzano, J., Caminero, J. A., Vidal, R., García, J. M., Blanquer, R. & Casals, M. (2009). Tuberculosis treatment adherence and fatality in Spain. *Respiratory Research,* 10(121).

CDC (2016). *Treatment for TB disease*. Available at: https://www.cdc.gov/tb/topic/treatment/tbdisease.htm (Accessed 6 June 2017).

Cele, L. P., Knight, S., Webb, E., Tint, K. & Dlungwane, T. (2016). High level of initial default among smear positive pulmonary tuberculosis in eThekwini health district, KwaZulu-Natal. *Southern African Journal of Infectious Diseases,* 31(2)**,** 41-43.

Chandra, M. & Mishra, V. (2017). *Clinical Approach to Infections in Pregnancy.* JP Medical Ltd.

Chandrasekaran, V., G., G. P., Subraman, R., Thomas, A., Jaggarajamma, K. & Narayanan, P. R. (2005). Default during the intensive phase of treatment under DOTS programme. *Indian Journal of Tuberculosis,* 52**,** 197-202.

Cherkaoui, I., Sabouni, R., Ghali, I., Kizub, D., Billioux, A. C., Bennani, K., Bourkadi, J. E., Benmamoun, A., Lahlou, O., Aouad, R. E. & Dooley, K. E. (2014). Treatment Default amongst Patients with Tuberculosis in Urban Morocco: Predicting and Explaining Default and Post-Default Sputum Smear and Drug Susceptibility Results. *PLoS ONE,* 9(4).

Chida, N., Ansari, Z., Hussain, H., Jaswal, M., Symes, S., Khan, A. J. & Mohammed, S. (2015). Determinants of Default from Tuberculosis Treatment among Patients with Drug-Susceptible Tuberculosis in Karachi, Pakistan: A Mixed Methods Study. *PLOS ONE,* 10(11).

Churchyard, G. J., Mametja, L. D., Mvusi, L., Ndjeka, N., Hesseling, A. C., Reid, A., Babatunde, S. & Pillay, Y. (2014). Tuberculosis control in South Africa: Successes, challenges and recommendations. *South African Medical Journal,* 104(3)**,** 244-248.

Culqui, D. R., Munayco, C., Grijalva, C. G., Cayla, J. A., Horna-Campos, O., Alva, K. & Suarez, L. (2012). Factors Associated With the Non-completion of Conventional Anti-Tuberculosis Treatment in Peru. *Archivos de Bronconeumología (English Edition),* 48(5)**,** 150-155.

Cunha, R., Maruza, M., Montarroyos, U. R., Coimbra, I., De B Miranda-Filho, D., Albuquerque, M. D. F., Lacerda, H. R. & Ximenes, R. a. A. (2017). Survival of people living with HIV who defaulted from tuberculosis treatment in a cohort, Recife, Brazil. *BMC Infectious Diseases,* 17(137).

Davies, P. D. O. (2003). The role of DOTS in tuberculosis treatment and control. *American Journal of Respiratory Medicine: Drugs, Devices, and Other Interventions,* 2(3)**,** 203-209.

Dodor, E. A. (2004). Tuberculosis treatment default at the Communicable Diseases Unit of Effia-Nkwanta Regional Hospital: a 2-year experience. *The International Journal of Tuberculosis and Lung Disease,* 8(11)**,** 1337-1341.

Dong, K., Thabethe, Z., Hurtado, R., Sibaya, T., Dlwati, H., Walker, B. & Wilson, D. (2007). Challenges to the Success of HIV and Tuberculosis Care and Treatment in the Public Health Sector in South Africa. *The Journal of Infectious Diseases,* 196(Supplement_3)**,** S491-S496.

Dooley, K. E., Lahlou, O., Ghali, I., Knudsen, J., Elmessaoudi, M. D., Cherkaoui, I. & El Aouad, R. (2011). Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. *BMC Public Health,* 11(140).

Ershova, J. V., Podewils, L. J., Bronner, L. E., Stockwell, H. G., Dlamini, S. & Mametja, L. D. (2014). Evaluation of adherence to national treatment guidelines among tuberculosis patients in three provinces of South Africa. *SAMJ: South African Medical Journal,* 104(5)**,** 362-368.

Fenner, L., Gagneux, S., Janssens, J.-P., Fehr, J., Cavassini, M., Hoffmann, M., Bernasconi, E., Schrenzel, J., Bodmer, T., Böttger, E. C., Helbling, P., Egger, M., Groups, F. T. S. H. I. V. C. & Molecular Epidemiology of Tuberculosis, S. (2012). Tuberculosis in HIV-Negative and HIV-Infected Patients in a Low-Incidence Country: Clinical Characteristics and Treatment Outcomes. *PLOS ONE,* 7(3).

Finlay, A., Lancaster, J., Holtz, T. H., Weyer, K., Miranda, A. & Van Der Walt, M. (2012). Patient- and provider-level risk factors associated with default from tuberculosis treatment, South Africa, 2002: a case-control study. *BMC Public Health,* 12(56).

Foster, N., Vassall, A., Cleary, S., Cunnama, L., Churchyard, G. & Sinanovic, E. (2015). The economic burden of TB diagnosis and treatment in South Africa. *Social Science & Medicine,* 130**,** 42-50.

Gafar, M. M., Nyazema, N. Z. & Dambisya, Y. M. (2014). Factors influencing treatment outcomes in tuberculosis patients in Limpopo Province, South Africa, from 2006 to 2010: A retrospective study. *Curationis,* 37(1)**,** 1-7.

García-Basteiro, A. L., Respeito, D., Augusto, O. J., López-Varela, E., Sacoor, C., Sequera, V. G., Casellas, A., Bassat, Q., Manhiça, I., Macete, E., Cobelens, F. & Alonso, P. L. (2016). Poor tuberculosis treatment outcomes in Southern Mozambique (2011–2012). *BMC Infectious Diseases,* 16(214).

Garrido, M. D. S., Penna, M. L., Perez-Porcuna, T. M., Souza, A. B. D., Marreiro, L. D. S., Albuquerque, B. C., Martínez-Espinosa, F. E. & Bührer-Sékula, S. (2012). Factors Associated with Tuberculosis Treatment Default in an Endemic Area of the Brazilian Amazon: A Case Control-Study. *PLOS ONE,* 7(6).

Gebremariam, G., Asmamaw, G., Hussen, M., Hailemariam, M. Z., Asegu, D., Astatkie, A. & Amsalu, A. G. (2016). Impact of HIV Status on Treatment Outcome of Tuberculosis Patients Registered at Arsi Negele Health Center, Southern Ethiopia: A Six Year Retrospective Study. *PLOS ONE,* 11(4).

Hasker, E., Khodjikhanov, M., Usarova, S., Asamidinov, U., Yuldashova, U., Van Der Werf, M. J., Uzakova, G. & Veen, J. (2008). Default from tuberculosis treatment in Tashkent, Uzbekistan; Who are these defaulters and why do they default? *BMC Infectious Diseases,* 8(97).

Herrero, M. B., Ramos, S., Arrossi, S., Herrero, M. B., Ramos, S. & Arrossi, S. (2015). Determinants of non adherence to tuberculosis treatment in Argentina: barriers related to access to treatment. *Revista Brasileira de Epidemiologia,* 18(2)**,** 287-298.

Hoa, N. B., Sokun, C., Wei, C., Lauritsen, J. M. & Rieder, H. L. (2012). Time to unsuccessful tuberculosis treatment outcome, Cambodia, China, and Viet Nam. *Public Health Action,* 2(1)**,** 15-20.

Holtz, T. H., Lancaster, J., Laserson, K. F., Wells, C. D., Thorpe, L. & Weyer, K. (2006). Risk factors associated with default from multidrug-resistant tuberculosis treatment, South Africa, 1999–2001. *The International Journal of Tuberculosis and Lung Disease,* 10(6)**,** 649-655.

Ifebunandu, N. A. & Ukwaja, K. N. (2012). Tuberculosis treatment default in a large tertiary care hospital in urban Nigeria: Prevalence, trend, timing and predictors. *Journal of Infection and Public Health,* 5(5)**,** 340-345.

IOM (2013). *MIGRATION & TUBERCULOSIS: A Pressing Issue*. Available at: http://www.iom.int/files/live/sites/iom/files/What-We-Do/docs/Migration-Tuberculosis-A-Pressing-Issue.pdf (Accessed).

IOM (2014). *Tuberculosis Prevention and Care for Migrants*. Available at: http://tbandmigration.iom.int/sites/default/files/publications/WHOIOM_TBmigration.pdf (Accessed 30 October 2010).

Jakubowiak, W., Bogorodskaya, E., Borisov, S., Danilova, I. & Kourbatova, E. (2009). Treatment interruptions and duration associated with default among new patients with tuberculosis in six regions of Russia. *International Journal of Infectious Diseases,* 13(3)**,** 362-368.

Jenkins, H. E., Ciobanu, A., Plesca, V., Crudu, V., Galusca, I., Soltan, V. & Cohen, T. (2013). Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova. *The International Journal of Tuberculosis and Lung Disease: The Official Journal of the International Union Against Tuberculosis and Lung Disease,* 17(3)**,** 373-380.

Kasozi, S., Clark, J. & Doi, S. a. R. (2015). Intermittent Versus Daily Pulmonary Tuberculosis Treatment Regimens: A Meta-Analysis. *Clinical Medicine & Research,* 13(3-4)**,** 117-138.

Kendall, E. A., Theron, D., Franke, M. F., Van Helden, P., Victor, T. C., Murray, M. B., Warren, R. M. & Jacobson, K. R. (2013). Alcohol, hospital discharge, and socioeconomic risk factors for default from multidrug resistant tuberculosis treatment in rural South Africa: a retrospective cohort study. *PloS One,* 8(12).

Khaliaukin, A., Kumar, A. M. V., Skrahina, A., Hurevich, H., Rusovich, V., Gadoev, J., Falzon, D., Khogali, M. & De Colombani, P. (2014). Poor treatment outcomes among

multidrug-resistant tuberculosis patients in Gomel Region, Republic of Belarus. *Public Health Action,* 4(Suppl 2)**,** S24-S28.
Khan, M. S., Fletcher, H. & Coker, R. (2016). Investments in tuberculosis research – what are the gaps? *BMC Medicine,* 14(123).
Kigozi, G., Heunis, C., Chikobvu, P., Botha, S. & Rensburg, D. V. (2017). Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. *International Journal of Infectious Diseases,* 54**,** 95-102.
Kizito, K. W., Dunkley, S., Kingori, M. & Reid, T. (2011). Lost to follow up from tuberculosis treatment in an urban informal settlement (Kibera), Nairobi, Kenya: what are the rates and determinants? *Transactions of The Royal Society of Tropical Medicine and Hygiene,* 105(1)**,** 52-57.
Kruk, M. E., Schwalbe, N. R. & Aguiar, C. A. (2008). Timing of default from tuberculosis treatment: a systematic review. *Tropical Medicine and International Health,* 13(2)**,** 703-712.
Kuchukhidze, G., Kumar, A. M. V., De Colombani, P., Khogali, M., Nanava, U., Blumberg, H. M. & Kempker, R. R. (2014). Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in Georgia. *Public Health Action,* 4(Suppl 2)**,** S41-S46.
Kulkarni, P. Y., Akarte, S. V., Mankeshwar, R. M., Bhawalkar, J. S., Banerjee, A. & Kulkarni, A. D. (2013). Non-Adherence of New Pulmonary Tuberculosis Patients to Anti-Tuberculosis Treatment. *Annals of Medical and Health Sciences Research,* 3(1)**,** 67-74.
Lackey, B., Seas, C., Stuyft, P. V. D. & Otero, L. (2015). Patient Characteristics Associated with Tuberculosis Treatment Default: A Cohort Study in a High-Incidence Area of Lima, Peru. *PLOS ONE,* 10(6).
Lee, J. Y. (2015). Diagnosis and Treatment of Extrapulmonary Tuberculosis. *Tuberculosis and Respiratory Diseases,* 78(2)**,** 47-55.
Macleod, W., Bor, J., Crawford, K. & Carmona, S. (2016). Analysis of Big Data for Better Targeting of ART Adherence Strategies : Spatial Clustering Analysis of Viral Load Suppression by South African Province, District, Sub-District and Facility (April 2014-March 2015). Washington, D.C.: World Bank.
Macpherson, P., Houben, R. M. G. J., Glynn, J. R., Corbett, E. L. & Kranzer, K. (2014). Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bulletin of the World Health Organization,* 92**,** 126-138.
Martin, L. R., Williams, S. L., Haskard, K. B. & Dimatteo, M. R. (2005). The challenge of patient adherence. *Therapeutics and Clinical Risk Management,* 1(3)**,** 189-199.
Masini, E. O., Mansour, O., Speer, C. E., Addona, V., Hanson, C. L., Sitienei, J. K., Kipruto, H. K., Githiomi, M. M. & Mungai, B. N. (2016). Using Survival Analysis to Identify Risk Factors for Treatment Interruption among New and Retreatment Tuberculosis Patients in Kenya. *PLoS ONE,* 11(10).
Massyn, N., Day, C., Peer, N., Padarath, A., Barron, P. & English, R. (2014). District Health Barometer 2013/14.
Massyn, N., Peer, N., English, R., Padarath, A., Barron, P. & Day, C. (2016). District Health Barometer 2015/16. Durban, South Africa.
Mohr, E., Cox, V., Wilkinson, L., Moyo, S., Hughes, J., Daniels, J., Muller, O. & Cox, H. (2015). Programmatic treatment outcomes in HIV-infected and uninfected drug-resistant TB patients in Khayelitsha, South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 109(7)**,** 425-432.

Moriguchi, S., Hayashi, Y., Nose, Y., Maehara, Y., Korenaga, D. & Sugimachi, K. (1993). A comparison of the logistic regression and the cox proportional hazard models in retrospective studies on the prognosis of patients with castric cancer. *Journal of Surgical Oncology,* 52(1)**,** 9-13.

Moyo, S., Cox, H. S., Hughes, J., Daniels, J., Synman, L., De Azevedo, V., Shroufi, A., Cox, V. & Van Cutsem, G. (2015). Loss from Treatment for Drug Resistant Tuberculosis: Risk Factors and Patient Outcomes in a Community-Based Program in Khayelitsha, South Africa. *PLoS ONE,* 10(3).

Mushayabasa, S. & Tapedzesa, G. (2015). Modeling Illicit Drug Use Dynamics and Its Optimal Control Analysis. *Computational and Mathematical Methods in Medicine,* 2015.

Muture, B. N., Keraka, M. N., Kimuu, P. K., Kabiru, E. W., Ombeka, V. O. & Oguya, F. (2011). Factors associated with default from treatment among tuberculosis patients in nairobi province, Kenya: A case control study. *BMC Public Health,* 11(696).

Neyrolles, O. & Quintana-Murci, L. (2009). Sexual Inequality in Tuberculosis. *PLOS Medicine,* 6(12).

Nglazi, M. D., Bekker, L.-G., Wood, R. & Kaplan, R. (2015). The impact of HIV status and antiretroviral treatment on TB treatment outcomes of new tuberculosis patients attending co-located TB and ART services in South Africa: a retrospective cohort study. *BMC Infectious Diseases,* 15(536).

Padayatchi, N., Loveday, M. & Naidu, N. (2014). Drug-resistant tuberculosis control in South Africa: scientific advances and health system strengthening are complementary. *Expert Opinion on Pharmacotherapy,* 15(15)**,** 2113-2116.

Pardeshi, G. S. (2010). Time of Default in Tuberculosis Patients on Directly Observed Treatment. *Journal of Global Infectious Diseases,* 2(3)**,** 226-230.

Peltzer, K. & Louw, J. S. (2014). Prevalence and factors associated with tuberculosis treatment outcome among hazardous or harmful alcohol users in public primary health care in South Africa. *African Health Sciences,* 14(1)**,** 157-166.

Pepper, D. J., Marais, S., Bhaijee, F., Wilkinson, R. J., Azevedo, V. D. & Meintjes, G. (2012). Assessment at Antiretroviral Clinics during TB Treatment Reduces Loss to Follow-Up among HIV-Infected Patients. *PLOS ONE,* 7(6).

Podewils, L. J., Bantubani, N., Bristow, C., Bronner, L. E., Peters, A., Pym, A. & Mametja, L. D. (2015). Completeness and Reliability of the Republic of South Africa National Tuberculosis (TB) Surveillance System. *BMC Public Health,* 15(765).

Pooran, A., Pieterson, E., Davids, M., Theron, G. & Dheda, K. (2013). What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa? *PLOS ONE,* 8(1).

Prado, T. N. D., Rajan, J. V., Miranda, A. E., Dias, E. D. S., Cosme, L. B., Possuelo, L. G., Sanchez, M. N., Golub, J. E., Riley, L. W. & Maciel, E. L. (2017). Clinical and epidemiological characteristics associated with unfavorable tuberculosis treatment outcomes in TB-HIV co-infected patients in Brazil: a hierarchical polytomous analysis. *The Brazilian Journal of Infectious Diseases,* 21(2)**,** 162-170.

Putera, I., Pakasi, T. A. & Karyadi, E. (2015). Knowledge and perception of tuberculosis and the risk to become treatment default among newly diagnosed pulmonary tuberculosis patients treated in primary health care, East Nusa Tenggara: a retrospective study. *BMC Research Notes,* 8(238).

Roy, N., Basu, M., Das, S., Mandal, A., Dutt, D. & Dasgupta, S. (2015). Risk factors associated with default among tuberculosis patients in Darjeeling district of West Bengal, India. *Journal of Family Medicine and Primary Care,* 4(3)**,** 388-394.

SA Department of Health (2014). National Tuberculosis Management Guidelines 2014. South Africa.
Sanchez-Padilla, E., Marquer, C., Kalon, S., Qayyum, S., Hayrapetyan, A., Varaine, F., Bastard, M. & Bonnet, M. (2014). Reasons for defaulting from drug-resistant tuberculosis treatment in Armenia: a quantitative and qualitative study. *The International Journal of Tuberculosis and Lung Disease,* 18(2)**,** 160-167.
Satti, S. B. R. & Kondagunta, N. (2016). Risk Factors for DOTS Treatment Default Among New HIV-TB Coinfected Patients in Nalgonda (Dist.) Telangana (State): A Case Control Study. *Indian Journal of Community Medicine,* 41(2)**,** 120-125.
Saunders, M. J. & Evans, C. A. (2016). Fighting poverty to prevent tuberculosis. *The Lancet Infectious Diseases,* 16(4)**,** 395-396.
Schneeweiss, S. (2006). Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiology and Drug Safety,* 15(5)**,** 291-303.
Sendagire, I., Loeff, M. S. V. D., Kambugu, A., Konde-Lule, J. & Cobelens, F. (2012). Urban Movement and Alcohol Intake Strongly Predict Defaulting from Tuberculosis Treatment: An Operational Study. *PLOS ONE,* 7(5).
Seunanden, T. & Day, C. (2014). The extent and impact of TB drug stockouts. *In:* Padarath, A. & English, R. (eds.) *South African Health Review 2013/14*. Durban, South Africa: Health Systems Trust.
Shean, K., Streicher, E., Piertesen, E., Symons, G., Van Zyl Smit, R., Theron, G., Lehloenya, R., Padanilam, X., Wilcox, P., Victor, T. C., Van Helden, P., Groubusch, M. P., Warren, R., Badri, M. & Oheda, K. (2013). Drug-Associated Adverse Events and Their Relationship with Outcomes in Patients Receiving Treatment for Extensively Drug-Resistant Tuberculosis in South Africa. *PLoS ONE,* 8(5).
Shringarpure, K. S., Isaakidis, P., Sagili, K. D. & Baxi, R. K. (2015). Loss-To-Follow-Up on Multidrug Resistant Tuberculosis Treatment in Gujarat, India: The WHEN and WHO of It. *PLOS ONE,* 10(7).
Sitienei, J., Kipruto, H., Mansour, O., Ndisha, M., Hanson, C., Wambu, R. & Addona, V. (2015). Correlates of default from anti-tuberculosis treatment: a case study using Kenya's electronic data system. *The International Journal of Tuberculosis and Lung Disease,* 19(9)**,** 1051-1056.
Statistics South Africa (2016). *Ekurhuleni*. Available at: http://www.statssa.gov.za/?page_id=1021&id=ekurhuleni-municipality (Accessed 2016-07-01).
Sterling, T. R., Pham, P. A. & Chaisson, R. E. (2010). HIV Infection—Related Tuberculosis: Clinical Manifestations and Treatment. *Clinical Infectious Diseases,* 50(Supplement 3)**,** S223-S230.
Takarinda, K. C., Harries, A. D., Mutasa-Apollo, T., Sandy, C. & Mugurungi, O. (2012). Characteristics and treatment outcomes of tuberculosis patients who "transfer-in" to health facilities in Harare City, Zimbabwe: a descriptive cross-sectional study. *BMC Public Health,* 12(981).
TB Care I (2014). International Standards for Tuberculosis Care. 3rd Edition ed, The Hague.
Thabane, L., Mbuagbaw, L., Zhang, S., Samaan, Z., Marcucci, M., Ye, C., Thabane, M., Giangregorio, L., Dennis, B., Kosa, D., Debono, V. B., Dillenburg, R., Fruci, V., Bawor, M., Lee, J., Wells, G. & Goldsmith, C. H. (2013). A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Medical Research Methodology,* 13(92).
Toczek, A., Cox, H., Du Cros, P., Cooke, G. & Ford, N. (2013). Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis

[Review article]. *The International Journal of Tuberculosis and Lung Disease,* 17(3)**,** 299-307.

Tola, H. H., Tol, A., Shojaizadeh, D. & Garmaroudi, G. (2015). Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. *Iranian Journal of Public Health,* 44(1)**,** 1-11.

Tupasi, T. E., Garfin, A. M. C. G., Kurbatova, E. V., Mangan, J. M., Orillaza-Chi, R., Naval, L. C., Balane, G. I., Basilio, R., Golubkov, A., Joson, E. S., Lew, W.-J., Lofranco, V., Mantala, M., Pancho, S. & Sarol, J. N. (2016). Factors Associated with Loss to Follow-up during Treatment for Multidrug-Resistant Tuberculosis, the Philippines, 2012–2014. *Emerging Infectious Diseases,* 22(3)**,** 491-502.

Weyer, K. (2007). *Case study: South Africa*. WHO, Available at: http://www.who.int/bulletin/volumes/85/5/06-036004/en/ (Accessed 7 June 2017).

WHO (2014). *Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014)*. Available at: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf?ua=1 (Accessed 27 January 2017).

WHO (2015). *Global Tuberculosis Report*. Available at: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1 (Accessed 30 June 2016).

WHO (2016). *Global Tuberculosis Report 2016*. Available at: http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1 (Accessed 26 January 2017 2017).

WHO (2017a). *The five elements of DOTS*. Available at: http://www.who.int/tb/dots/whatisdots/en/files/598/en.html (Accessed 17 May 2017).

WHO (2017b). *What is DOTS (Directly Observed Treatment, Short Course)*. Available at: http://www.searo.who.int/tb/topics/what_dots/en/ (Accessed 17 May 2017).

Wood, R., Johnstone-Robertson, S., Uys, P., Hargrove, J., Middelkoop, K., Lawn, S. D. & Bekker, L.-G. (2010). Tuberculosis transmission to young children in a South African community: modeling household and community infection risks. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America,* 51(4)**,** 401-408.

APPENDIX

Ethics Clearance Certificate

R14/49 Ms Betenai Moyo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161183

NAME: (Principal Investigator)	Ms Betenai Moyo
DEPARTMENT:	School of Public Health
PROJECT TITLE:	Factors Associated with Loss to Follow-Up in HIV-Uninfected Tuberculosis Patients in Ekurhuleni North Sub-District
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Tendesayi Kufa-Chakezha
APPROVED BY:	Professor P Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/11/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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. 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 November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical)

Principal Investigator Signature Date 8/12/16

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Table A1: List of variables and the coding used

Variable	Coding/Format
Participant ID	Number
Age at TB diagnosis (years)	Continuous
Age at TB diagnosis (years)	0: 18-34 1: 35+
Length of treatment (months)	Continuous
Length of treatment (months)	0: Less than 6 months 1: 6-9 months 2: 9-12 months 97: Unknown/missing
Time to LTFU (months)	Continuous
Time to LTFU (months)	0: Less than 2 months 1: 2-4 months 2: 4-6 months 3: 6-12 months 97: Unknown/missing
Time to change of treatment phase (months)	Continuous
Time to change of treatment phase (months)	0: Less than 2 months 1: 2-4 months 2: 4-6 months 3: 6-12 months 97: Unknown/missing
Sex	1: Male 2: Female
Episode type	1: New 2: Re-treatment
TB site, smear and culture status	1: Pulmonary smear or culture positive 2: Pulmonary smear and culture negative 3: Non-pulmonary
Change of treatment phase	0: No 1: Yes 3: Unknown/missing
Treatment outcome	1: Success 3: LTFU 4: MDR-TB 6: Death 7: Treatment failure
Success or poor outcome	1: Success 2: Poor outcome
Loss to follow-up	0: No LTFU 1: LTFU
Treatment clinic	3: A 4: B 5: C 6: D 8: E

Variable	Coding/Format
	9: F 11: G 12: H 14: I 15: J 16: K 17: L 22: M 24: N 27: O 29: P 30: Q 31: R
Patient burden at treatment clinic	1: Low burden 2: High burden
Treatment start date	Date
Date of change of treatment phase	Date
Date of most recent clinic visit	Date
Date of treatment completion	Date
Exit date	Date