PREDICTORS OF DEATH AMONG TUBERCULOSIS PATIENTS WHILE ON TREATMENT IN LOCAL HEALTH FACILITIES IN FRANCISTOWN

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A mini-thesis submitted in partial fulfilment of the requirements for the degree of Master in Public Health at the School of Public Health, University of the Western Cape

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Keywords: Tuberculosis, Mortality, Risk, Prevalence, Incidence, HIV, Predictors, Co-morbidity, Electronic TB register, survival analysis.
ABBREVIATIONS

AOR: Adjusted Odds Ratio
AFB: Acid- Fast Bacilli
AIDS: Acquired immune deficiency syndrome
ART: Anti-retroviral therapy
CI: Confidence interval
CPT: Cotrimoxazole preventive therapy
DHMT: District Health Management Team
DOT: Directly observed therapy
DOTS: Directly observed therapy short Course
EPTB: Extra pulmonary tuberculosis
ETR: Electronic TB Register
HIV: Human immunodeficiency virus
HR: Hazard ratio
IPT: Isoniazid preventive therapy
IQR: Interquartile range

MDG: Millennium Development Goal
MDR-TB: Multi-drug resistant tuberculosis
MOH: Ministry of Health
MTB: Mycobacterium tuberculosis
OR: Odds ratio
PLWH: People Living With HIV
PTB: Pulmonary tuberculosis
SES: Socio-economic status
WHO: World Health Organization
XDR-TB: Extreme/extensively drug resistant tuberculosis
DEFINITIONS OF KEY TERMS

Completed treatment: TB patient who has completed the intensive and continuation phases of TB treatment; may be cured or not.

Cured: completion of the TB treatment with a smear negative result at 6/8 month

Death: refers to the death while on the TB treatment with confirmed TB at the time of the death; regardless of cause.

Demographic factors: refers to the age and gender.

Extensive- Drug Resistance TB (XDR- TB): resistance to rifampicin, isoniazid and at least one of the other (second line) anti-TB drugs.

Extra- pulmonary TB: refers to TB of organs other than the

Multi- Drug Resistance TB (MDR- TB): resistance at least to the two most effective first line TB drugs (rifampicin and isoniazid).

New Patient: a patient who never had treatment for TB or who has taken anti-TB treatment for less than one month, or patient previously treated and cured (two or more years ago) who is diagnosed with TB again.

Pulmonary TB: refers to the disease involving the lung parenchyma.

Retreatment patient (relapse): a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriology positive TB.

Treatment classification: is based on the site of TB, may be pulmonary TB or extra- pulmonary TB.

Treatment group: refers to new patient or retreatment patient.

Treatment outcomes: include-completed treatment, death, sputum smear conversion and treatment failure.
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ABSTRACT

Background: Botswana has one of the highest TB incidence rates in the world. Tuberculosis in those without HIV infection accounts for 13% of adult mortality and in those living with TB and HIV in Botswana account for 40% of annual adult mortality. Francistown is a health district with TB mortality rates in excess of 5% of diagnosed TB patients yearly. The aim of this study was to assess patient related factors and early warning signs (predictors) of death among TB patients on treatment in Francistown clinics in order to identify possible interventions.

Methodology: A retrospective case-control study design was used in this study. The records of all patients treated for TB from January 2010 to November 2015 who met the study inclusion criteria were extracted from the district electronic register (ETR). Socio-demographic variables, clinical variables and treatment outcome were collected and analysed. Univariate and multivariate logistic regression techniques were used to assess the predictors of death and the Kaplan Meier plot to determine time to death while on treatment.

Result: A total of 1718 participants were included in the study. The median age of the study population was 35 years (IQR: 29, 42). Of the study population, 56% were male. Most of the participants had pulmonary TB (78%). There was a very high HIV prevalence among the study population (74%). About 44% of participants had smear results at the start and at the completion of TB treatment. Of the 1718 participants 161 (95% CI 8.0-10.8) died during the course of TB treatment. Univariate analysis showed HIV status, extra-pulmonary TB and a history of TB treatment default to be associated with earlier death. Multivariate analysis of selected variables showed that being older (≥ 55 years old), HIV-positive, having a history of TB and extra-pulmonary TB are independent predictors of death while on TB treatment. The overall median time to death was 52 days. Lack of HIV-related intervention during TB treatment was a significant independent predictor of time to death (adjusted HR = 1.79; 95% CI 1.03 – 3.1; p = 0.037).

Conclusion: Of the 1718 adult patients treated for TB in Francistown clinics from January 2010 to November 2016, 161 (9%) died while on treatment. The predictors of death identified in the study include, prior history of TB infection, Extra-Pulmonary TB, HIV status, HIV-related intervention and over 55 years of age. Gender was not a predictor of death in this study. Their overall median time to death in the study was 52 days. Patients on treatment for the first time with no previous history of TB lived on average 150 days on TB treatment. All TB patients with HIV co-infection that did not receive Antiretroviral Therapy (ART) and or Cotrimoxazole Preventive
Therapy (CPT) died during the intensive phase of TB treatment. More than half of all deaths recorded in this study occurred during the intensive phase of TB treatment. After adjusting for gender, age, treatment classification, treatment group and HIV status and the lack of HIV-related interventions during TB treatment was the significant predictor of earlier death among patients with TB/HIV co-infection in this study.
CHAPTER 1

BACKGROUND

1.1 Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB) but can affect other sites in the body (extra-pulmonary TB (EPTB)). Tuberculosis is an airborne disease which is spread when people who are sick with pulmonary TB expel bacteria by coughing or sneezing. About 5 to 15% of the estimated two billion people infected with *M. tuberculosis* will develop TB disease during their lifetime (WHO, 2014).

1.2 Global Tuberculosis Epidemiology

In 1993, the World Health Organization (WHO) declared TB a global emergency of avoidable death in developing countries (WHO, 1993). A third of the world’s population are infected with tuberculosis (WHO, 2014). In 2014, there were 9.6 million TB infections (approximately six million were new) of which: 5.4 million men, 3.2 million women and one million children. About 12% of all reported new TB infections in 2014 occurred in HIV-positive people (WHO, 2014). Of the global TB cases reported, 95% were recorded in developing countries and 98% of annual global TB-related deaths occurred in these countries (MOH, 2011). More than two thirds of TB cases occur in the economically productive 15 to 50 years age group, and the disease is responsible for 25% of all avoidable deaths in developing countries (Woldeyohannes et al., 2011). Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a profound increase in the number of TB cases, with incidence rates increasing threefold over the last decade in some countries (MOH, 2011). The high prevalence of TB in some sub-Saharan African countries is attributed to the decreased levels of immunity among the HIV-positive population (Zachariah et al., 2002). Tuberculosis is ranked alongside HIV as a leading cause of death worldwide, having killed 1.5 million people in 2014 (WHO, 2014). Despite the huge financial and human investments in TB (disease diagnosis, care and treatment), it continues to be a global public health challenge.

1.3 Epidemiology of Tuberculosis in Botswana
Tuberculosis is a public health emergency in Botswana; a country with one of the highest TB notification rates in the world. In 2011, the estimated TB incidence was close to four times the global equivalent at 455 per 100000 persons (MoH, 2013). Botswana experienced a decline in TB notification rates from 506 per 100000 in 1975 to 199 per 100 0000 in 1989 (MoH, 2007). However, the TB incidence rates more than doubled by the 1990s making the WHO rank Botswana among the countries with the highest TB incidence rates in the world (MoH, 2012). Tuberculosis is responsible for 13% of all adult mortality and 40% of mortality among people living with HIV (PLWH) in Botswana (MOH, 2007, Etard et al., 2006). Figure 1.1 below, illustrates the positive correlation between HIV prevalence and the TB notification rate in the Botswanan population.

Figure 1.1: Trends in TB case notification rates and HIV prevalence in Botswana (Source: BNTP Annual Reports 2013).

The Botswana AIDS Impact Survey estimated HIV prevalence at 18.5% among the population aged 18 months and above (Botswana AIDS Impact Survey IV, 2013). The population aged between 35 and39 and 45 and 49 years had the highest prevalence estimated at 44% and 42% respectively (Botswana AIDS Impact Survey IV, 2013). Among the poorer parts of the population, around 64% of HIV-positive patients were found to be infected with TB (MoH, 2013). Based on the WHO clinical staging, the Botswana National Antiretroviral Treatment (ART) programme has listed TB infection as a major opportunistic infection requiring the commencement of ART irrespective of CD4 count. Due to the co-morbidities of TB and HIV, the national ART and TB
programmemes have been working closely in an effort to address these dual epidemics. The overall treatment success rate for 7254 notified patients in 2013 was 73% (WHO, 2014). The treatment success rate among HIV-positive patients co-infected with TB was lower at 71% (WHO, 2014). The mortality rate amongst the HIV-positive patients co-infected with TB was almost 12%, compared to the 7% amongst the HIV-negative patients (The Global Fund, 2015).

1.4 Tuberculosis in Francistown

Francistown is among the health districts with a high case notification rate (Figure 1.2) and a high TB mortality rate in excess of 5% (The Global Fund, 2015). The unpublished Francistown District Health Management Team report documented TB mortality from 2010 to 2014 at 5%, 11%, 9%, 7%, 12% respectively.

![Figure 1.2: Case notifications rates per 100000 population in the districts (2012 and 2013) (Source: The Global Fund, 2015: Botswana TB and HIV Concept Note).](image)

1.5 Problem Statement
Over the years, the Botswana Ministry of Health has shown great commitment in the fight against TB through the adoption of many strategies including: the Directly Observed Therapy (DOT) which was adopted and implemented throughout the country; improved diagnosis of TB through training of laboratory staff (MoH Botswana, 2013), and the introduction of innovative technology (Gene Xpert) to rapidly diagnose TB (Agizew et al., 2012). Health care workers were trained on case detection and management of TB. Other strategies implemented include the provision of community based TB care, free TB care and treatment, and the linkage of the TB and HIV programmes.

Despite the interventions to curb the threat of TB driven by HIV infection, the prevalence of TB and the associated mortality remains very high (MoH Botswana, 2013). Tuberculosis is a curable disease that should not necessarily result in death. However, many deaths are recorded and appear to be increasing related to HIV (MoH Botswana, 2013). The provision of free HIV and TB treatment in all public hospitals and clinics has not reduced mortality among patients especially those co-infected with TB and HIV. Access to health services in Botswana (particularly in Francistown) is made easy by the availability of facilities within proximity to residential areas. Clinics are within an eight kilometre radius, simplifying access, especially in the towns and cities. Tuberculosis awareness has greatly improved through the collaborative efforts of different community based organisations that are actively working to support the TB programme through community mobilization, TB related health education and promotion, and contact tracing. Patients presenting for TB care and treatment at the clinics have diverse characteristics in terms of age, co-morbidities, socio-economic status, habits or lifestyle, educational status, TB classification (pulmonary or extra-pulmonary), TB severity (drug sensitive or drug resistant TB), smear microscopy results (smear negative or positive), TB grouping (new or retreatment), and TB treatment outcome (completed treatment, died or defaulted treatment). These different patient characteristics impact on death as a possible TB treatment outcome.

Despite the significant investment in TB care and treatment, many adult patients treated for TB in Francistown clinics died before completing treatment. No study has been done in Botswana to characterize patients that died while on TB treatment. This study investigate TB reported deaths among adult patients treated between January 2010 and November 2015 to identify patient-related factors and early warning signs (predictors) of death among TB infected patients accessing care and treatment in the Francistown clinics.
1.6 Study setting

The Botswanan health care delivery system is based on the primary health care model that is made up of public, private for-profit, private non-profit and traditional medical practices. The public sector makes up about 98% of the health facilities (AHO, 2016). These facilities include three referral hospitals, 15 general hospitals, 17 primary hospitals, two mission hospitals, three private hospitals, 289 clinics, 350 health posts, and more than 900 mobile stops. Thus, 85% of the population is located within eight kilometres of a health facility (AHO, 2016). Botswana has a well-established free national TB and HIV treatment programme for citizens, while non-citizens pay for health care services at public health facilities. In 2011 Botswana implemented nationwide six-months Isoniazid Preventive Therapy (IPT) among PLWH who have not started ART following the demonstration of the preventive advantage of IPT against TB in PLWH in clinical trials (Bucher et al., 1999, Woldehanna et al., 2004, Mwinga et al., 1998).

Francistown is the second largest city in Botswana with a population of about 100,000 people. It is situated in the north-eastern part of Botswana about 90 kilometres from the Zimbabwean border. The Francistown population access medical services at facilities comprising one referral hospital, 25 public clinics, 13 health posts and 22 private clinics. The public clinics are under the administration of the Francistown District Health Management Team (DHMT). The study will focus on the public health facilities within Francistown city, which are located within the different residential settlements around the city. The TB programme uses DOT and community TB strategies. Patients infected with TB receive treatment and care in the clinic within their residential area. The TB record for each patient is kept at the local clinic and an aggregated TB record from all the clinics is captured in the District electronic TB register (ETR) under the supervision of the District TB Focal person.

1.7 Purpose

The purpose of the study was to analyse patient-related factors and early warning signs (predictors) of death among patients infected with TB who are on treatment in Francistown. Findings from this study could help inform health care providers about patients on TB treatment who need close monitoring and special attention so as to prevent the possibility of this group of patients dying while on treatment. The findings could also be useful for the TB Programme Managers who review TB treatment protocols. Also, information from this study could potentially equip staff
caring for these patients at the local clinics to identify and closely monitor patients showing early warning signs indicative of high risk of dying while on treatment.

1.8 Summary

Tuberculosis continues to be a global emergency and accounts for millions of deaths annually. Botswana like other countries with a high prevalence of HIV, has witnessed an increase in the number of TB cases and increasing number of death associate with TB. Tuberculosis treatment is free, with patients accessing care from the Public Health facilities. This study will analyse patient-related factors and early warning signs (predictors) of death among patients infected with TB in Francistown using TB records from the Francistown district ERT. The next chapter will focus on reviewed literature relevant to the subject matter of this study.
CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Reported mortality among tuberculosis (TB) patient is still high in many countries around the world. In this chapter relevant information about TB mortality in the literature is discussed. Findings from other researchers working on mortality among patients infected with TB were reviewed in terms of the nature of the study population, study setting, and main findings. The review focused on the epidemiology of TB, causes of TB mortality and the risk or predictors of death among patients while on TB treatment.

2.2 Epidemiology of Tuberculosis

Tuberculosis remains one of the world’s deadliest communicable diseases (WHO, 2014) and is ranked among the top ten causes of death worldwide especially in Asia and Africa (WHO, 2008 & 2009). The disease is reported to be responsible for 26% of avoidable adult deaths in developing countries (Bloom & Murray, 1992). In an effort to reduce the mortality associated with TB, the Millennium Development Goals (MDG) prioritised the reduction of death associated with TB by half by 2015 (WHO, 2010). In 2013, an estimated 1.5 million people died from the disease (WHO, 2014). The global case fatality is reported to be between 7% and 35% (Chou et al., 2014). In the era of HIV/AIDS, the weakening of the immune system in HIV-positive individuals has greatly contributed to the increase in the case fatalities (Zachariah et al., 2002, MOH, 2007, Etard et al., 2006). The majority of TB reported cases are in South Asia and the African regions, with sub-Saharan Africa carrying the largest burden of the disease (UN, 2010). Botswana has one of the world’s highest incidences of TB (NTP report, 1999, Kenyo et al., 1999).

2.3 Causes of TB mortality

The World Health Organisation (WHO) defines TB mortality as any TB cases dying during treatment regardless of the cause (WHO, 1994). Over the years, several studies have been done on the subject of TB mortality focusing on the cause of death among TB cases, the risk factors for death while on treatment, and predictors of death among HIV-positive and HIV-negative populations. Many of these studies have reported that other conditions apart from TB may be the
cause of death while a patient is on TB treatment (Cayla et al., 2004, Venkatarama et al., 1998, Bustamante-Monte et al., 2000, Harries et al., 2001, Gustafson et al., 2007). Korenromp et al. (2009) and Saraceni et al. (2008) reported that death due to TB may actually be under-documented or misclassified depending on the method used to estimate mortality. At present, deaths in treatment cohorts cover a small subset of all estimated TB deaths, as deaths are missed among patients who are never diagnosed, those who default or fail treatment, and among patients with untreated recurrent TB or TB sequelae (Korenromp et al., 2009). Some of the deaths in the TB treatment cohort are TB-related or caused primarily by TB infection, while other reported deaths are clearly not TB-related e.g. death from other co-morbidities (cancer, hypertension, diabetes, kidney and liver failure) or other disease complications, automobile accident or suicide. For this study, the cause of death in the TB treatment cohort will not be considered. The treatment outcome among TB patients on treatment will be grouped as either completed treatment and alive or died while on TB treatment.

2.4 Risk factors or predictors of death among TB patients

Several risk factors or predictors have been found to be associated with death among patients on TB treatment. The literature review in this section will discuss these risk factors or predictors of death under the following headings demographic factors (age, gender), socio-economic factors (homelessness, malnutrition, level of education and patient’s behaviour), and clinical conditions including - nature of TB (Pulmonary TB (PTB) or Extra-Pulmonary TB (EP-TB)), severity of TB disease (Multi-Drug Resistant TB (MDR-TB) and Extensively Drug Resistant TB (XDR-TB)), category of patient (new or retreatment), sputum smear result, and co-morbidity. Review of different works by other researchers working on death among TB patients will be discussed with a focus on their study setting, timing of the study, study design and main findings. This study will look at how these risk factors affect mortality among patients on TB treatment in Francistown clinics.

2.5 Demographic factors

2.5.1 Age

Different TB mortality studies in South Africa (Pepper et al., 2015, Nigel et al., 2014), the United States (Pratt et al., 2011), Queensland, Australia (Walpola et al., 2003), Thailand (Anunnatsiri et al., 2005), Taipei-Taiwan (Yena et al., 2012, Wu et al., 2014), Israel (Shuldiner et al., 2014),
Shanghai, China (Xin et al., 2009) and Saudi Arabia (Abouzeid et al., 2013) all showed a positive correlation between TB mortality and age. In a study conducted in Mexico, Najera-Ortiz et al. (2008) reported that those aged 45 years and over have a higher risk of TB mortality. Ekaterina et al. (2012) also reported age above 45 years as an independent predictor of death in a large multicentre retrospective cohort study among MDR-TB patients on DOT programmeme in Russia, Latvia, Estonia, Peru and the Philippines. In a retrospective cohort study conducted over seven years in an aging population in a city in Taiwan, advancing age was associated with death while on TB treatment (Lin & Yen, 2015). The two South African studies, one among Platinum miners (Nigel et al., 2014) and a retrospective cohort study among TB patients in a community with high prevalence of HIV (Pepper et al., 2015), also reported age as a predictor of death.

### 2.5.2 Gender

Gender disparities in the epidemiology of TB disease and TB treatment outcomes have been reported by different researchers. The impact of gender on TB treatment outcome in the literature has revealed inconsistent results (Feng et al., 2012). Some studies reported that males are at a higher risk of dying while on TB treatment in India, Israel, Brazil, China, Singapore Taiwan (Santha et al., 2002, Shuldiner et al., 2014, Duarte et al., 2009, Xin et al., 2009, Low et al., 2009, Feng et al., 2012). In the prospective observational study in Taiwan, Feng et al. (2012) reported that a greater proportion of the study population that died were older males with more co-morbidities, who smoked more, and had a lower two-month sputum conversion rate compared to their female counterparts.

Contrary to most studies, a retrospective cohort study conducted in South Africa reported females to be at a higher risk for death among TB patients (Pepper et al., 2015). A prospective cohort study of patients who began treatment for TB between June 1999 and May 2000 in Spain reported that gender was not associated with fatality (Cayla et al., 2004).

### 2.6 Socio-economic status

Socio-economic status (SES) has been shown to impact on health-seeking behaviour and thus impact on the treatment outcome of many chronic disease conditions (Kim et al., 2014, Elgart et al., 2014). The history of TB has shown a strong link between the disease and SES, with the disease historically being associated with poverty and people of a lower SES (Holtgrave & Crosby, 2004, Figueroa-Munoz & Ramon-Pardo, 2016, Harling et al., 2008, Cramm et al., 2011).
assumption still remains true in many impoverished communities. However, TB is not primarily the disease of the poor or people of low SES alone. In a cohort study in Norway to determine the regional and socio-economic differences in TB incidence and mortality, Liestol et al. (2009) reported that the difference in all-cause mortality is partly linked to socio-economic factors. Lin and Yen (2015) however reported a strong correlation between SES and TB mortality among the elderly TB patients in Taiwan.

2.6.1 Malnutrition

Malnutrition and TB are both problems of considerable magnitude in most of the underdeveloped regions of the world and closely linked with SES (Gupta et al., 2009). It has been found that malnourished patients with TB have delayed recovery and higher mortality rates than well-nourished patients (Gupta et al., 2009). Malnutrition has been proven to be a risk factor for TB mortality in different settings around the world (Gustafson et al., 2007; Santha et al., 2002; Zachariah et al., 2002; Malto et al., 2006; Zahar et al., 2001). In a prospective cohort study in Malawi, Zachariah et al. (2002) reported that moderate to severe malnutrition was a risk factor associated with early mortality. In another prospective study in Guinea-Bissau, Gustafson et al. (2007) reported an association between malnutrition and death among HIV-positive and HIV-negative patients. In a prospective cohort study among hospitalised patients in north-east Brazil, low serum albumen was associated with in-hospital death due to TB (Maltos & Moreira Lemos, 2006). Maltos and Moreira Lemos (2006) report similar findings as Okamura et al. (2013) who conducted a prospective cohort study in Japan and reported hypoalbuminemia as a predictive risk factor for in-hospital mortality in patients with TB.

2.6.2 Level of education

Education has also been recognized as an economic status marker; in this case, lower education may be associated with lack of resources, overcrowding and unsanitary conditions (Chung-Delgado et al., 2015). The level of education of patients has an impact on adherence to treatment and better understanding of the disease condition and treatment (Hoa et al., 2004, Sanchez-Barriga, 2015). Level of education among TB patients is reported to have a positive correlation with mortality (Najera-Ortiz et al., 2008, Lin & Yen, 2015, Yena et al., 2012, Delgado et al., 2015). Hoa et al. (2004) associated a lower level of education with poor understandings of TB, leading to poor outcomes including death. In a cohort study conducted in China among MDR-TB
cases, Sun et al. (2002) found that a lower level of education among the study population was associated with the risk of mortality. This is similar to the findings among MDR-TB population in Peru (Delgado et al., 2015). In a study in Mexico, individuals not completing elementary school showed to have a higher risk of dying from Pulmonary TB (Sanchez-Barriga, 2015).

2.6.3 Patient’s behaviour

Patient behaviour is influenced by their SES status. Patient behaviour is an important factor that could promote or adversely affect health as well as influence treatment outcome. Patient behaviour has been shown to influence TB test-seeking behaviour (Ford et al., 2009), compliance to treatment, default, treatment failure and death (Santha et al., 2000, Cayla et al., 2004, Pablos-Mendez et al., 1996, Barker et al., 2006, Waitt & Squire, 2011). Santha et al. (2002) reported delays in care seeking by patients in India as an important risk factor for death among male patients treated in a directly observed treatment strategy (DOTS). In a cross-sectional study among the Peruvian Amazon community, Ford et al. (2009) corroborated findings from Santha et al. (2002). In an observational study among HIV-infected patients co-infected with TB in New York City, Pablos-Mendez et al. (1996) reported that patients who started TB treatment after a 1-month delay died. In a cohort study in a rural South African setting with high burden of TB by Waitt and Squire (2006), treatment delay due to visiting a traditional healer had dire consequences for the patients. Literature also reports alcohol and substance misuse as risk factors for death among TB patients (Waitt & Squire, 2011, Cayla et al., 2004). Contrary to other study reports on the effect of alcohol consumption on treatment outcomes and mortality, an Iranian study among TB-HIV patients reported no significant association between smoking, drug and alcohol abuse (Tabarsi et al., 2012).

2.6.4 Homelessness

Homelessness is associated with people of low SES. In a study to determine risk factors for death among TB patients in a rural settlement in Russia where the WHO global TB control strategy was being implemented, Dewan et al. (2004) reported that high TB fatality was linked to homelessness among the study population. Findings of a prospective cohort study on status of treatment completion and fatality among TB patients in Spain also reported an association between homelessness and fatality (Cayla et al., 2004). In a retrospective study in the city of Sao Paulo in Brazil between 2002 and 2013 to determine the impact of homelessness on unsuccessful outcome
of treatment of pulmonary TB, Ranzani et al. (2016) reported homelessness as an important contributor to treatment failure including death.

The SES factors discussed above impact on the health seeking behaviour of patients as well as the treatment outcomes including death. In this study, the effects of SES on TB mortality are not investigated due to the challenge of collecting these data retrospectively. These variables are either not recorded or poorly documented at the clinics.

2.7 Clinical conditions

Patients present with different types of TB disease which have varying impacts on the treatment outcome, including death. The presentations of TB disease, PTB or EPTB, MDR-TB or XDR-TB, and other co-morbidities are the different factors that could complicate diagnosis, delay or prolong treatment and impact on the possible treatment outcomes. These clinical presentations pose a serious challenge especially in resource limited settings.

2.7.1 Nature and severity of TB infection

The type and site of the TB infection have varying impacts on the treatment outcomes. Extra-pulmonary TB (EPTB) and drug-resistant TB (MDR-TB and XDR-TB) are associated with higher mortality rates than PTB. The WHO estimated 450,000 new cases of MDR-TB in 2012 (WHO, 2013). Dalton et al. (2012) and Mitnick et al. (2008) reported that XDR-TB account for 6% of drug-resistant TB cases. Multidrug-resistant TB and XDR-TB forms of TB are difficult to treat and require many months of therapy (Bonilla et al., 2008) using multiple drugs with toxic effects (Chung-Delgado et al., 2011). Extra-pulmonary TB is difficult to diagnose in most resource-constrained settings and often results in patients being misdiagnosed and starting TB treatment when they are critically ill (Ya Diul et al., 2001). Thus, many TB patients with EPTB or drug resistant TB have a bad prognosis and an increased likelihood of dying.

In a retrospective study among adult TB patients in an inner-city hospital in the United States between 1995 and 2001, Kourbatova (2006), reported EPTB as a persistent problem that is associated with high mortality. In another study Kourbatova et al. (2012) reported EPTB as an independent predictor of death among 1768 patients treated for TB in Estonia, Latvia, Philippines, Russia and Peru between 2000 and 2004. In another study in a high HIV prevalence population in
sub-Saharan Africa, a higher TB case fatality rate was associated with EPTB especially among smear-positive patients (Ya Diul et al., 2001).

Reports from different studies have demonstrated a significant association between drug-resistant TB and mortality among TB patients on treatment in both HIV-positive and HIV-negative study populations. Pablos-Mendez (1996) reported MDR as a predictive factor for higher mortality among TB patients in an observational study in New York City. Santha et al. (2002) reported similar finding as Pablos-Mendez et al. (1996) in a population based study in Tiruvallur district of India involving 209 villages and nine urban clusters from 1999 to 2000. In a larger retrospective cohort study in Israel involving 4555 participants between 2000 to 2010, MDR was reported as a risk factor for death among the participants (Shuldiner et al., 2014). Other studies in Turkey (Babalik et al., 2013), Vietnam (Quy et al., 2006), Peru (Chung-Delgado et al., 2015, Kawai et al., 2006), and Estonia (Lockman et al., 2001) showed a positive correlation between MDR-TB and increased fatality. Gandhi et al. (2006) reported a higher fatality rate among patients with XDR-TB in a South African study conducted in the KwaZulu-Natal province. Of the 1539 participants in the study, MDR-TB was diagnosed in 221 participants of whom 53 had XDR-TB. Fifty two of 53 patients with XDR-TB died, with median survival of 16 days from time of diagnosis (Gandhi et al., 2006).

2.7.2 Category of patients

Patients with TB can be classified or grouped as new (no previous history of TB disease) or retreatment (previous history of TB disease). Some studies (Santha et al., 2002, Quy et al., 2006, Jonnalagada et al., 2011, Chung-Delgado et al., 2015, Field et al., 2014) have reported a higher mortality rate among retreatment patients compared to patients that have no previous history of TB infection/treatment. In a study carried out in South Africa by Field et al. (2014) where they studied the timing, rates and causes of death within the TB programmeme, they found the percentage of deaths among the retreatment patients to be twice that of the new patients. Their findings are in agreement with findings from Jonnalagada (2011) who reported a relative risk of mortality of 1.98 among patients with previous history of TB that are on TB treatment in Andhra Pradesh, South India. Santha et al. (2002) also found that previous history of TB was a risk factor for death in South India. Babalik et al. (2013) also noted that patients with a previous history of TB, and third month positive microscopy were at a higher risk of death in a case-control study in
Turkey between 2006 and 2009. Also, Chung-Delgado et al. (2015) found that there was a higher risk of death among MDR-TB with previous history of TB in a retrospective cohort study in Peru. Contrary to most reported findings, Albuquerque et al. (2014) conducted a prospective cohort study among PLWH on TB treatment in Brazil and reported that a previous history of TB does not predispose them to a higher risk of death while on TB treatment.

2.7.3 Co-morbidity

Studies have reported the impact of co-morbidity as a predictor of death among patients on TB treatment (Chou et al., 2014, Tarika & Tekabe, 2015, Agbor et al., 2014, Pacharee et al., 2012, Nigel et al., 2014, David et al., 2010, Xin et al., 2009, Shuldiner et al., 2014). The impact of HIV infection in worsening the TB disease and TB/HIV-related mortality has been well documented (Horne et al., 2010, WHO, 2008, Lawn & Wood, 2011, Chou et al., 2014). The effect that HIV infection has on patients with TB disease can be measured by the high TB notification rates and the reported case fatalities in settings with high prevalence of HIV (Pepper et al., 2015). Countries with high HIV infection rates report that HIV is one of the main reasons for failure to achieve TB control targets (WHO, 2004). In a meta-analysis, Straetemans et al. (2011) reported a threefold increase in the percentages of death among TB patients who were HIV-positive.

Other co-morbidities that have been reported to be associated with death among TB patients on treatment include- hypertension (Erhobor et al., 2006), malignancy (Chou et al., 2014, Fernanda et al., 2005), influenza (Sibongile et al., 2015), liver cirrhosis (Erhobor et al., 2006), renal failure (Chou et al., 2014, Erhobor et al., 2006, Fielder et al., 2002), malnutrition (Erhobor et al., 2006, Gustafson et al., 2007, Okamura et al., 2013, Santha et al., 2002, Zachariah et al., 2002, Malto et al., 2006, Zahar et al., 2001), heart failure (Erhobor et al., 2006), and Diabetes mellitus (Subbanna et al., 2011, Baker et al., 2011, Faurholt, 2013, Fielder et al., 2002).

2.8 TB Mortality in Botswana

Literature on TB mortality in Botswana is scant, though the national TB and HIV programmeme continues to report a high incidence of TB cases especially among HIV-positive people. Due to the devastating effect of HIV/TB co-infection (Rana et al., 2000, Etard et al., 2006, MOH, 2007), the TB and HIV programmeme have been linked in all health facilities across the country. Oeltmann et al. (2008) conducted a TB treatment outcome study among children in Gaborone and Francistown and reported that younger children (less than five years old) with TB were twice as
likely to have death as an outcome of TB treatment compared to older children. In a post-mortem study conducted among 128 predominantly HIV-positive hospitalized patients in Francistown, TB was diagnosed in 40%; and it accounted for 36% of death in the study group (Ansari et al., 2002). Though the study sample was small, the study established the importance of TB as an opportunistic infection and cause of death among the HIV-positive population (Ansari et al., 2002). In another study conducted in 1997 by Steen et al. (2001) using data from all health facilities (excluding private sector), TB was reported to be the main cause of death among in-patients (16%). These studies conducted in Botswana highlight that TB is responsible for reported mortality among patients with TB and within the HIV-positive population. However, none of the studies looked into the predictors of death among TB patients.

2.9 Review of research methodology

Most of the studies on TB mortality were retrospective studies relying on past patient medical records from the clinics or hospitals (Agbor et al., 2014, Ansari et al., 2002, Erhobor et al., 2006), or records from the Regional or District TB records (Horne et al., 2010, Kaplan et al., 2014, Chung-Delgado et al., 2015, Lin et al., 2006). These retrospective studies reported limitations relating to the unavailability of relevant TB patient data for analysis and incomplete patient medical records. Some of the studies (Bustamante-Monte et al., 2000, Najera-Ortiz et al., 2008) were conducted in a single centre in a region thus their results cannot be generalized to other regions. Most of the studies did not consider people who defaulted treatment in their analysis hence the reported mortality rates may be higher than what was reported as some of the defaulters may have died (Najera-Ortiz et al., 2008). Some other researcher used the prospective cohort study design to find the association between different patients’ demographic and clinical conditions with mortality among patients with TB (Albuquerque et al., 2014, Matos et al., 2006, Cayla et al., 2004).

2.10 Aim and objectives of this study

The previous sections of this chapter provided a review of the different factors that contribute to mortality among patient on TB treatment in different settings. This study assessed patient-related factors and early warning signs (predictors) of death among patients with TB who were treated in Francistown clinics.

The objectives of the study were to:
1. Determine the socio-demographic profile of adults (≥18 years of age) TB patients on treatment.
3. Investigate early predictors of time to death among patients on TB treatment.

2.11 Summary
This chapter reviewed a selected array of relevant literatures on the factors that contribute to TB mortality and predictors of death among patients on TB treatment. Chapter Three will highlight the research methods used in this study.
Chapter 3
Research Methodology

3.1 Introduction
This chapter highlights the research methods used in this study. This epidemiological study employed quantitative research methods to collect and analyse patient-related variables that are routinely recorded at the clinics during the treatment and care of TB patients. These data are recorded on the Facility TB Treatment Card as part of the routine standard treatment procedures of patients enrolled for TB treatment. The facility TB treatment records for all the clinics are captured in District Electronic Tuberculosis Register (ETR). This study attempted to identify risk factors or predictors of death among TB patients on treatment in all clinics in Francistown. The study consists of secondary data abstracted from the ETR from January 2010 to November 2015. No contact was made with the patients during the study period. Statistical analyses were conducted using STATA (version 13.1) software.

3.2 Research design
A retrospective case-control study design was used in this study. All TB records from January 2010 to November 2015 were reviewed and data extracted for all eligible patients from the district ETR. This study design was chosen as it can yield important scientific findings with relatively little time, money, and effort compared with other study designs (Schulz & Grimes, 2002). The case-control study design allowed the determination of the association of different predictor variables to mortality within the study population. This study design was ideal in the Francistown context as the health facilities have a well-established TB programme with patients’ TB treatment records documented in a facility TB register. The information in the facility paper based TB registers from all the clinics is entered into the ETR at District level. In this study, the cases (patients who died while on TB treatment) were compared with the controls (patients with TB who completed treatment within the study time frame). Different researchers have used the case-control study design to measure the association of different variables with treatment outcomes in patients with TB in different settings (Duarte et al., 2009, Babalik et al., 2013, Oeltmann et al., 2008, Boccia et al., 2011). Parhar et al. (2015) used a case-control study design in determining if early TB death among cases in the province of Alberta in Canada was associated with increased TB transmission.
In the Parhar et al. (2015) study, cases and controls were matched using age, sex, population group, and positive/negative smear status

### 3.3 Study population

The study population was made up of all patients ranging from 18 years and above with documented confirmed TB diagnosis by routine Acid-Fast Bacillus (AFB) smear microscopy, culture, MTB/RIF Xpert result or chest x-ray that were registered for TB treatment in Francistown clinics, and were resident in Francistown during the treatment period. For the purposes of this study and access to treatment data, data from patients residing in the study area until death or completion of treatment were included. Absence of nationally linked electronic records across the country did not allow for inclusion of patients who were transferred out of the study area.

**Cases:** All patients who had a treatment outcome of “died” while on treatment between January 2010 and November 2015.

**Controls:** All patients who had a treatment outcome of “completed treatment” while on treatment between January 2010 and November 2015.

**Inclusion criteria:**

- All forms of TB cases (pulmonary TB (PTB), Multidrug Resistant TB (MDR) and Extensively Drug Resistant TB (XDR) with or without any other co-morbidity were included in the study
- Patients who had a treatment outcome of either “died” while on treatment or “completed” treatment
- Patients residing in the study area for the duration of treatment or until death occurred.

**Exclusion criteria:**

- Patients with incomplete records (treatment outcome unknown)
- Transfer out patients whose follow-up data is not accessible

  (NOTE: ETR databases across health districts are not linked in Botswana).

### 3.4 Sampling strategy
No sampling was carried out. All eligible patients on TB treatment from January 2010 to November 2015 were included in the study. This time frame gave information on the characteristics of TB mortality in the Francistown health facilities during the study period.

3.5 Sample size consideration

A census sampling approach was conducted. All eligible TB cases recorded in the ETR within the period of the study were included in the data analyses.

3.6 Data sources

The source of data for the study was the District ETR. Individual patient data from the facility-paper based TB register are entered into the ETR. The ETR is under the supervision of the District TB coordinator who oversees the activities of the TB programme in all the health facilities in the district.

3.7 Data collection

The study involved collection of TB patient related data using a data extraction form (Appendix 4) by the researcher with the assistance of the District TB Coordinator. Data collection involved extraction of secondary data that are documented during TB treatment at the clinic. Data extracted from the ETR using the data extraction sheet were entered into an access database that is password protected. Data from the access database were later exported to an excel spreadsheet for analyses. Patient identifiers (Clinic Registration numbers) were stored in a lockable cabinet that the researcher alone has access to as a way of protecting the confidentiality of patients. No contact was made with participants nor were their medical records reviewed. Data used in this study were data collected under the Botswana National Tuberculosis programme. The different variables of interest collected are:

- Year of registration
- Health facility
- Age
- Gender
- Occupation (Student, Health Care Worker, Miner/Ex-miner and other)
• Patient weight
• Treatment classification (Pulmonary TB or Extra-pulmonary TB)
• Treatment group - New or retreatment (failure, default, relapse and other)
• Sputum smear results (at months: 0, 2, 3, 6 and 8)
• HIV status
• HIV-related intervention-Antiretroviral Therapy (ART), Isoniazid Preventive Therapy (IPT) and Cotrimoxazole prophylaxis (CPT)
• Treatment outcome (dead or alive)

3.8 Data analyses

Data exported into an excel spreadsheet was imported in STATA (version 13.1) for analysis. Descriptive analyses were used to describe the frequency and percentage of demographic variables (age, gender and Occupation) and clinical variables (disease classification, treatment group, sputum smear result, HIV status, HIV treatment, IPT history, Cotrimoxazole history, TB treatment outcome, weight at initiation and continuation phase of TB treatment). Categorical data were presented as percentages while continuous data were presented by the means and standard deviations for normally distributed variables; skewed data were presented as medians, maximum and minimum values and interquartile ranges. Association between TB death and selected categorical variables was done using Chi-square or Fishers’ exact tests where appropriate. Wilcoxon sign rank test was used to compare medians for continuous variables using selected groups. Univariate and multivariate logistic regression techniques were used to assess the predictors of death. Variables with p<0.2 in the univariate were included in the multivariate model. Gender and treatment group were included a priori. The variables used included: demographic variable (age, gender) and patient clinical variables (disease classification, treatment group, HIV status, HIV-related intervention, ART, CPT and IPT). Univariate and multivariate Cox regression analyses and Kaplan Meier curves were conducted to identify predictors of time to death while on TB treatment. All variables from univariate analyses were included a priori into the time to death multivariate model. The 95% Confidence intervals and p-values for these variables were computed. A p-value < 0.05 was considered statistically significant in the study.
3.9 Validity and reliability

In general, the quality and method of collection of secondary data used for research purposes are not under the control of the researcher (Sorensen et al., 1998). Completeness and accuracy of the secondary data is very important as it affects the reliability of the results. The reliability of the District ETR was verified by comparing randomly selected patient information in the ETR with the facility based TB register. The ETR was chosen as the source of data as it is the system used by the National TB programme to aggregate TB reports from the different facilities. Individual patient TB related variables that are recorded on the facility TB register are entered into the ETR. The ETR is used to analyse and generate quarterly and annual TB report for the district.

Internal validity of the study was enhanced by selecting the cases and controls from the same study population (all enrolled TB patients in all the local clinics within the study period). Selection and chance bias was minimized by including all the patients who meet the inclusion criteria within the study period in the cases and controls. Prior to data analyses, data cleaning was carried out to check for any abnormal and inconsistent data. The effect of confounding was evaluated by using multivariate regression analysis to find out the impact of individual variables on TB mortality.

3.10 Ethical considerations

Ethics approval was sought and obtained from the Senate Research Committee at the University of the Western Cape (Appendix 1) and the Botswana Human Research Development Committee at the Ministry of Health (Appendix 2) before conducting the research. Permission to extract patient data from the Francistown district ETR was obtained from the District Health Management Team (Appendix 3). No contact was made with participants and the study posed minimal risk to the patient whose records were abstracted. The research collected data that are relevant to the objectives of the study, the information was not used in such a way that could violate the dignity of the patient whose record is abstracted. Participants’ personal identifiers were not used during the study proceedings and in the manuscript. Data collected for analyses was kept secured on a computer that is password protected and was only available to study investigators.

3.11 Summary
This chapter outlined the method employed in this study. This epidemiological study employed quantitative research methods to collect and analyse patient-related variables that are routinely recorded at the clinics during the treatment and care of TB patients. The next chapter presents the findings of this study.
CHAPTER 4
RESULTS

4.1 Introduction

This chapter presents the results of the study. The characteristics of the study population, including socio-demographic and clinical variables are described in summary descriptive statistics using tables and figures. Also presented, are the univariate and multivariate analyses of the predictors of death and the time to death among the study population using the Kaplan Meier plot.

4.2 Socio-demographic characteristics of study participants

A total of 1718 participants were included in the study across 18 health facilities in Francistown, Botswana. Ten year age categories were used in this study. The median age of the participants was 35 years (IQR: 29, 42). Males accounted for 56.3% of the study population. Table 4.1 shows the summary of the key socio-demographic and clinical characteristics of the study participants.

Weight and occupation of the patients were inconsistently documented in the ETR, thus they were not included in the analysis nor reported.

Table 4.1: Socio-demographic and clinical characteristics (number and percentage) of patients enrolled on TB treatment in Francistown clinics, 2010-2015.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Participants</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>750</td>
<td>43.7</td>
</tr>
<tr>
<td>Male</td>
<td>968</td>
<td>56.3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>median age = 35 years (Q1, Q3: 29, 42)</td>
<td></td>
</tr>
<tr>
<td>18 – 24</td>
<td>65</td>
<td>3.8</td>
</tr>
<tr>
<td>25 – 34</td>
<td>178</td>
<td>10.4</td>
</tr>
<tr>
<td>35 – 44</td>
<td>663</td>
<td>38.6</td>
</tr>
<tr>
<td>45 – 54</td>
<td>502</td>
<td>29.2</td>
</tr>
<tr>
<td>55 – 64</td>
<td>235</td>
<td>13.7</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>75</td>
<td>4.4</td>
</tr>
</tbody>
</table>
### Table 4.1: (Continue)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Participants</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of Treatment Initiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>379</td>
<td>22.1</td>
</tr>
<tr>
<td>2011</td>
<td>342</td>
<td>19.9</td>
</tr>
<tr>
<td>2012</td>
<td>353</td>
<td>20.6</td>
</tr>
<tr>
<td>2013</td>
<td>291</td>
<td>16.9</td>
</tr>
<tr>
<td>2014</td>
<td>227</td>
<td>13.2</td>
</tr>
<tr>
<td>2015</td>
<td>126</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>980</td>
<td>57.0</td>
</tr>
<tr>
<td>Ex-miner</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>734</td>
<td>42.7</td>
</tr>
<tr>
<td><strong>HIV Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>424</td>
<td>24.7</td>
</tr>
<tr>
<td>Positive</td>
<td>1270</td>
<td>73.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>24</td>
<td>1.4</td>
</tr>
</tbody>
</table>

#### 4.2.1 Age by Treatment year

There was an observed increase in the age of TB patient on treatment during the study period and a significant difference in the median age across the 6 years study period ($p = 0.0034$, Figure 4.1) from median age of 36.0 in 2010 to median age of 39.2 in 2015.
Figure 4.1: Age distribution of TB patients in Francistown clinics, 2010-2015.

4.2.2 Age distribution by Gender

The study population was made up of mostly males especially in the older age groups (> 45 years). Females were marginally (53%) more than the males within the 18 to 34 years group. Within the 35-44 year age group, an equal proportion of both males and females was represented. However, males represent 64.3% of the study population within the age group of 45 years and above.

4.3 Clinical characteristics of study participants

Throughout the years included in the study, majority of the study participants had Pulmonary TB. The proportion of Pulmonary to extra-pulmonary TB did not significantly change over time (p = 0.494; Figure 4.2).
**Figure 4.2:** Distribution of TB patients by treatment classification (anatomical site of TB infection) in Francistown clinics, 2010-2015.

### 4.3.1 Treatment classification (anatomic site of TB infection)

Across the years of treatment included in the study (2010-2015), the median age of participants diagnosed with extra-pulmonary TB was always higher than those diagnosed with pulmonary TB. The highest median age for both EP-TB and PTB in the study population was recorded in 2014.

There was a statistically significant association between gender and type of TB or site of TB infection among the study population ($p = 0.002$). A higher proportion of EPTB was recorded among females compared to males in the study population (Figure 4.4).
4.3.2 Treatment group (new/retreatment—previous history of TB infection)

There was a statistically significant association between treatment group and gender (p = 0.003), age (p = 0.001), and HIV status (p = 0.026) among the study population (Table 4.2). The ratio of men to women was 1.2:1 among the new treatment group while it was 2:1 among the retreatment groups. Association between age and new treatment group was significant with the highest association noticed within the 25-34 year and 35-44 year age group. Also, a high association between HIV status and new treatment group was noticed.
Table 4.2: Characteristics of the study participants by treatment group, Francistown clinics, 2010-2015.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group n (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New</td>
<td>Retreatment</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>682 (90.9)</td>
<td>68 (9.1)</td>
</tr>
<tr>
<td>Male</td>
<td>835 (86.3)</td>
<td>133 (13.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median (Q1, Q3)</td>
<td>34 (28, 42)</td>
</tr>
<tr>
<td>18 - 24</td>
<td>54 (83.1)</td>
<td>11 (16.9)</td>
</tr>
<tr>
<td>25 - 34</td>
<td>165 (92.7)</td>
<td>13 (7.3)</td>
</tr>
<tr>
<td>35 - 44</td>
<td>606 (91.4)</td>
<td>57 (8.6)</td>
</tr>
<tr>
<td>45 - 54</td>
<td>430 (85.7)</td>
<td>72 (14.3)</td>
</tr>
<tr>
<td>55 - 64</td>
<td>197 (83.8)</td>
<td>38 (16.2)</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>65 (86.7)</td>
<td>10 (13.3)</td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>389 (91.7)</td>
<td>35 (8.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>1106 (87.1)</td>
<td>164 (12.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>22 (91.7)</td>
<td>2 (8.3)</td>
</tr>
</tbody>
</table>

*P-value generated from Wilcoxon Rank Sum Test

4.3.3 TB Smear result

Table 4.3 shows the smear result for the study population. A significant proportion of the patients had no smear result at month two, three and at treatment completion.
Table 4.3: TB smear result of study participants on TB treatment in Francistown clinics, 2010-2015.

<table>
<thead>
<tr>
<th>Month</th>
<th>New Alive</th>
<th>Negative N (%)</th>
<th>Positive N (%)</th>
<th>No result N (%)</th>
<th>Total N (%)</th>
<th>Retreatment Alive</th>
<th>Negative N (%)</th>
<th>Positive N (%)</th>
<th>No result N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0</td>
<td>94 (52%)</td>
<td>490 (32%)</td>
<td>712 (47%)</td>
<td>315 (21%)</td>
<td>1517</td>
<td>47 (23%)</td>
<td>114 (57%)</td>
<td>40 (20%)</td>
<td>180</td>
<td>201</td>
</tr>
<tr>
<td>Month 2</td>
<td>820 (54%)</td>
<td>44 (3%)</td>
<td>653 (43%)</td>
<td>1517</td>
<td>18</td>
<td>7 (3.9%)</td>
<td>47 (23%)</td>
<td>114 (57%)</td>
<td>40 (20%)</td>
<td>201</td>
</tr>
<tr>
<td>Month 3</td>
<td>628 (41%)</td>
<td>0</td>
<td>559 (59%)</td>
<td>1517</td>
<td>-</td>
<td>22 (11%)</td>
<td>2 (1%)</td>
<td>177 (88%)</td>
<td>21</td>
<td>201</td>
</tr>
<tr>
<td>Month 6</td>
<td>628 (41%)</td>
<td>0</td>
<td>559 (59%)</td>
<td>1517</td>
<td>-</td>
<td>19 (9%)</td>
<td>0</td>
<td>182 (91%)</td>
<td>21</td>
<td>201</td>
</tr>
<tr>
<td>Month 8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1517</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4.4 shows the TB smear results and treatment outcome for the retreatment TB group (patients with a history of TB).

Table 4.4: TB Smear results and treatment outcome for the retreatment group of TB patients in Francistown clinics, 2010-2015.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Smear Results at 3 months of TB Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive</td>
<td>Negative N (%)</td>
</tr>
<tr>
<td>Alive</td>
<td>94 (52%)</td>
<td>7 (3.9%)</td>
</tr>
<tr>
<td>Died</td>
<td>2 (9.5%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>96 (47.8%)</td>
<td>8 (4.0%)</td>
</tr>
</tbody>
</table>

Table 4.5 shows the TB smear results and treatment outcome for the new TB treatment group (patients with no history of TB).

Table 4.5: TB Smear results and treatment outcome for the new treatment group of TB patients in Francistown clinics, 2010-2015.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Smear Results at 2 months of TB Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive</td>
<td>Negative N (%)</td>
</tr>
<tr>
<td>Alive</td>
<td>801 (58%)</td>
<td>42 (3%)</td>
</tr>
<tr>
<td>Died</td>
<td>19 (14%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Total</td>
<td>820 (54%)</td>
<td>44 (3%)</td>
</tr>
</tbody>
</table>
4.3.4 HIV-related intervention to prevent TB

A large proportion of the HIV-positive TB patients had a record of being on ART, taking CPT, had history of IPT or a combination of these interventions to reduce the risk of TB infection (Figure 4.4).

![Figure 4.4: HIV-related intervention to prevent TB infection in HIV-positive patients on TB treatment in Francistown clinics, 2010-2015.](image)

### 4.4 Predictors of death during TB treatment

A total of 161 of the 1718 participants (9.37%; 95% CI 8.0-10.8) died during the course of TB treatment with more patients in the 35 to 54 year age group dying.

A univariate analysis of the study data showed that HIV status, extra-pulmonary TB and treatment default were associated with death while on TB treatment among the study population (Table 4.6). Multivariate analyses showed that being older, HIV-positive, having unknown HIV, being a retreatment patient, and having extra-pulmonary TB were independent predictors of death while on TB treatment in the study population (Table 4.6).
**Table 4.6:** Univariate and multivariate analyses of the characteristics of 1718 tuberculosis patients associated with death during TB treatment, Francistown clinics, 2010-2015.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment Outcome</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>death (N, %) OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>750</td>
<td>76 (10.1)</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>968</td>
<td>85 (8.8)</td>
<td>0.85 (0.62 - 1.18)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 – 34</td>
<td>243</td>
<td>18 (7.41)</td>
<td>1</td>
</tr>
<tr>
<td>35 – 54</td>
<td>1165</td>
<td>95 (8.15)</td>
<td>1.10 (0.66 - 1.87)</td>
</tr>
<tr>
<td>≥55</td>
<td>310</td>
<td>48 (8.6)</td>
<td>2.29 (1.29 – 4.05)</td>
</tr>
<tr>
<td><strong>HIV Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>424</td>
<td>19 (4.5)</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>1270</td>
<td>138 (10.9)</td>
<td>2.60 (1.59 – 4.25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>24</td>
<td>4 (16.7)</td>
<td>4.26 (1.32 – 13.70)</td>
</tr>
<tr>
<td><strong>Treatment Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>1517</td>
<td>140 (9.2)</td>
<td>1</td>
</tr>
<tr>
<td>Retreatment</td>
<td>201</td>
<td>21 (10.5)</td>
<td>1.15 (0.71 – 1.86)</td>
</tr>
<tr>
<td><strong>Treatment classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>384</td>
<td>51 (13.3)</td>
<td>1</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>1334</td>
<td>110 (8.3)</td>
<td>1.70 (1.20 – 2.43)</td>
</tr>
<tr>
<td><strong>Retreatment classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>1517</td>
<td>143 (9.4)</td>
<td>1</td>
</tr>
<tr>
<td>Fail</td>
<td>27</td>
<td>2 (7.4)</td>
<td>0.37 (0.05 – 2.80)</td>
</tr>
<tr>
<td>Relapse</td>
<td>162</td>
<td>14 (8.6)</td>
<td>1.00 (0.57 – 1.76)</td>
</tr>
<tr>
<td>Defaulter</td>
<td>12</td>
<td>2 (16.7)</td>
<td>7.03 (2.2 – 22.4)</td>
</tr>
</tbody>
</table>
4.5 Predictors of time to death while on TB treatment

Time to death which is defined as the time from initiation of TB treatment to time of death while on treatment was analysed for all the 161 patients that died. The Cumulative mortality is shown in Figure 4.6. The overall median time to death in the study population was 52 days (Q1, Q2: 15 – 112) with approximately 50% of the cases dying within 2 months of starting TB treatment.

![Figure 4.5: Kaplan Meier plot showing the cumulative mortality during TB treatment in Francistown clinic, 2010-2015.](image)

A univariate cox regression showed that there were no statistically significant differences in time to death by gender (HR = 0.92; 95% CI 0.67 – 1.26) and treatment classification (HR = 1.02; 95% CI 0.73 – 1.43). Participants with no history of TB showed to be more likely to die within 5 months of being on treatment (HR 1.36 95% CI 0.66 - 2.17. p= 0.187) though this observation was not statistically significant. After adjusting for gender; age at start of TB treatment, treatment class (pulmonary vs extra-pulmonary), treatment group (new vs retreatment), and HIV status, lack of HIV-related intervention during TB treatment was a significant independent predictor of time to death (adjusted HR = 1.79; 95% CI 1.03 – 3.1; p = 0.037). All participants without any form of HIV-related interventions died within 60 days of starting TB treatment (Figure 4.7)
Summary

Among the 1718 adult patients on TB treatment in Francistown health facilities from January 2010 to November 2016 that were included in this study, a total of 161 (9.37%) died while on treatment. Analysis of the study data showed that 56% of the TB patients were male. Analysis of the result showed a significant difference in the median age across the study period (P=0.0034) from a median age of 36 years in 2010 to a median age of 39 years in 2015. Students make up 57% of the study population.

Predictors of mortality while on treatment include-being 55 years or older, previous history of TB, HIV-positive status, unknown HIV status and HIV-related interventions. In this study, gender was not a predictor of death. Antiretroviral therapy and CPT were found to be protective of death in the study. More than half of deaths recorded in this study occurred during the intensive phase of TB treatment.

After adjusting for gender, age, treatment classification, treatment group and HIV status, lack of HIV-related interventions (ART and CPT) during TB treatment was a significant independent predictor of time to death among patients with TB/HIV co-infection in this study. Chapter five will discuss the implication of these findings.
CHAPTER 5
DISCUSSION

5.1 Introduction
This chapter presents the discussion of the important findings of this study. The discussion focuses on the predictors of death and the predictors of the time to death among the TB patients who died while on TB treatment. The chapter will also discuss the interventions that were protective to death among the TB patients in the study. Other important findings of the study relating to smear result, gender, and treatment group and treatment classification will also be discussed.

5.2 Predictors of death among patients on TB treatment in Francistown
The mortality rate among TB patient in Francistown during 2010 to 2015 was 9.37%. Many factors have been associated with mortality among people on TB treatment in different settings. In this study the predictors of death among the patients on TB treatment in Francistown clinics include advancing age, HIV status, EPTB, a history of TB, treatment relapse and default, and HIV-related interventions. These important predictors of death are discussed below.

5.2.1 Prior TB infection
Univariate analysis showed that treatment group did not impact on death while on treatment. However, multivariate analysis showed a significant association between treatment group and mortality making retreatment group an important predictor of death. The mortality risk among the study population with previous history of TB after multivariate analysis was seven-fold higher among participants with a history of defaulting TB treatment. In this study, participants with a history of TB treatment failure and TB relapse showed to be at a higher risk of death. This finding corroborates reports from other studies (Santha et al., 2002, Najera-Ortiz et al., 2008, Kawai et al., 2006, Field et al., 2014, Babalik et al., 2013, Jonnalagada et al., 2011 and Quy et al., 2006). It was observed in this study that many of the patients that completed TB treatment could not be classified as cured of TB as most did not have smear results at the completion of treatment. The potential implication of this, is that patients that are not cured after treatment will later develop TB again especially if they have a condition that weakens the immune system. Patients with poor adherence to TB treatment have a higher probability of developing MDR-TB (Sonnenberg et al., 2001, Zignol
et al., 2007), an aggressive form of TB which predisposes the patients to increased risk of death (Tocwue et al., 2005) while on treatment. Among the retreatment group, TB defaulters had the highest risk of mortality while on treatment. Some of the factors reported to be responsible for defaulting TB treatment in the literature include-patients’ economic situation (Johansson et al., 1996), socio-economic status (Belo et al., 2011) and poor adherence (Zellweger et al., 1998). In a Botswanan study reported by Talbor et al. (1993), not knowing that death could occur from TB and not receiving counselling before the start of TB treatment were risk factors for defaulting treatment.

5.2.2 Extra Pulmonary Tuberculosis

Extra-Pulmonary Tuberculosis was a predictor of death while on TB treatment in this study. This finding is in agreement with findings of TB studies in Nepal (Sreeramareddy et al., 2008) and Ethiopia (Silesh et al., 2013). Extra-Pulmonary Tuberculosis is difficult to diagnose in many resource limited setting including Botswana which usually results in patients starting TB treatment in advanced state of the infection. Other co-morbidities also complicate the diagnosis of EPTB further delaying the start of treatment.

5.2.3 HIV co-infection

Univariate and multivariate analyses both show that being HIV-positive or having an unknown HIV status are predictors of death among TB patients in this study. Co-morbidities have been linked to increased mortality among TB patients on treatment in many previous studies (Chou et al., 2014, Tarika & Tekabe, 2015, Agbor et al., 2014, Pacharee et al., 2012, Nigel et al., 2014, David et al., 2010, Xin et al., 2009, Shuldiner et al., 2014). Among TB patients, HIV co-infection has been reported to increase the risk of mortality (Cayla et al., 2004, Horne et al., 2010, WHO, 2008, Lawn & Wood, 2011, Chou et al., 2014). In this current study, there was a positive association between the 85.7% of patients who died with HIV-positive status; a finding that supports findings of the Botswana Ministry of Health (MOH, 2007) and other Botswana TB researchers’ results (Ansari et al., 2002, Steen et al., 2001). This finding gives credence to the need to screen for HIV in patients diagnosed with TB and have their HIV status documented in the TB records.

5.2.4 HIV-related intervention
Result from this study showed that CPT and ART were effective in reducing mortality among TB patients. This finding further supports the assertion of many other reports regarding the protective ability of CPT and ART among TB patients co-infected with HIV (Zachariah et al., 2003, Mwaungulu et al., 2004, Woldehanna et al., 2004, Straetemans et al., 2011, Van’t Hoog et al., 2012). Though the HIV treatment guidelines outline the importance of CPT in reducing TB infection and mortality among PLWH and HIV patients with immunological and virological failures, analysis of the study data showed that a significant proportion of the patients did not have documented use of CPT in their TB record.

5.2.5 Age

Age was not a predictor of death in the unadjusted and univariate analyses, but age became a predictor of death in the multivariate analysis. Among the study population, being older than 55 years was predictive of death. Advancing age as a predictor of death has been reported in many studies (Sun et al., 2015, Pepper et al., 2015, Lin et al., 2015, Pratt et al., 2011). Some of the factors contributing to higher mortality among the older TB patients on treatment in other studies includes reduced access to health services (Xin et al., 2009), malnutrition (Zachariah et al., 2002, Gustafson et al., 2007, Matos et al., 2006), poor socio-economic status (Dewan et al., 2004, Liestol et al., 2009, Cayla et al., 2004) and HIV and other co-morbidities (Anunnatsiri et al., 2005, Ruiz-Navarro et al., 2005, Shuldiner et al., 2014). Access to health services is not thought to influence mortality among the patients in this study as health care is free and health facilities are accessible within an eight kilometre radius of the population.

5.2.6 Gender

Gender is an important factor in the epidemiology of many diseases including TB infection, progression to TB disease and mortality. In this study, gender was not a predictor of death or time to death. This finding is in agreement with findings from a study by Cayla et al. (2004), but contrary to many other studies. Many research findings have associated being male with a higher risk of death and time to death while on treatment (Santha et al., 2002, Schuldiner et al., 2014, Duarte et al., 2009).

5.3 Predictors of time to death among patients on TB treatment in Francistown.
In this study, the risk of mortality was higher among patients in the first two months of TB treatment with approximately half of death occurring in the intensive phase of TB treatment. The overall median time to death was 52 days. This finding is similar to reported timing of mortality during TB treatment in a range of other studies (BirLie et al., 2015, Mathew et al., 2006, Walpola et al., 2003, Pepper et al., 2015, Harries et al., 2009, Ismail & Bulgiba, 2013). After adjusting for gender, age, treatment classification, treatment group, and HIV status, ART and CPT administration during treatment among TB patients co-infected with HIV were independent predictors of time to death in this study. All HIV-positive patients who were not on ART and or CPT died before completion of the two-month intensive phase of TB treatment. The short survival probability among TB/HIV co-infected patients in the study could be attributed to late presentation for treatment or institutional delays in initiating treatment, a weakened immune system, possible immune reconstitution inflammatory syndrome (IRIS), poor tolerability of the anti-tuberculosis drug or other co-morbidities. Further research is needed to solidify these speculations. Findings from this study clearly demonstrate the value of initiating ART on all HIV-positive patients infected with TB as soon as possible. The study also demonstrates the protective property of CPT among PLWH.

5.4 Other interesting observations.

Some interesting findings were made during the analyses of the study data. These findings could be potentially useful in patient care and management thereby contributing to better treatment outcomes among TB patients. These findings are presented below-

5.4.1 Extra-pulmonary Tuberculosis among the study population

A significantly higher proportion of EPTB occurred among female TB cases compared to males in the study population. This finding seems to be a new finding with no known study in Botswana reporting any association between female gender and EPTB. Different studies in India (Peto et al., 2009), United States (Holmes et al., 1998) and Denmark (Zhang et al., 2011) all reported an association between EPTB and being female. Some of the factors thought to be associated with the high prevalence of EPTB among female include endocrine factors (Forssbohm et al., 2008) and smoking (Sreeramareddy et al., 2008 and Chiang et al., 2007). In this study, variables relating to smoking or tobacco use were not routinely documented in the TB treatment records, thus
association of smoking to a higher prevalence of EPTB in the female participants in the study could not be established.

5.4.2 Smear result

More than half of the study participants were diagnosed or started TB treatment without a documented smear result. The proportion of missing smear results in the study is much higher than those reported in other studies (Pepper et al., 2015, Shuldiner et al., 2014, Dewan et al., 2004, Xin et al., 2009). Studies in different settings have reported diverging results about the association of sputum smear positivity or negativity at the start of TB treatment to the risk of dying while on TB treatment (Harries et al., 1998, Ekaterina et al., 2012, Pepper et al., 2015, Xin et al., 2009). Though an alarming 85% of the patients that died while on TB treatment had no smear result either at the start of TB treatment or at the completion of the intensive phase of TB treatment; no inference could be drawn between smear result and death in the study population.

5.4.3 HIV co-infection and HIV-related interventions among study population

A high proportion of the study population (73.9%) were co-infected with HIV while on TB treatment between 2010 and 2015. This finding is in line with the findings of other researchers that reported a close association between TB and HIV infection (Shuldiner et al., 2014, Straetemans et al., 2011). TB/HIV co-infection have been documented to affect TB treatment outcome and mortality (Babalik et al., 2013, Albuquerque et al., 2014). This finding lends support to the assertion that all TB patients need to be tested for HIV and have a documented HIV status while on TB treatment. A large proportion of HIV-positive patients that were treated for TB in the study period had documented records of HIV-related interventions of either receiving one or a combination of antiretroviral therapy (ART), Isoniazid preventive therapy (IPT) or Cotrimoxazole prophylaxis (CPT). These interventions have been proven to reduce the risk of TB infection and mortality among HIV-positive individuals (Pepper et al., 2015, Manosuthi et al., 2008, Zachariah et al., 2001, Zachariah et al., 2003). In a bid to reduce the incidence of TB infection among PLWH, the BNTP recommends IPT for all HIV-positive individuals without active TB infection for a period of six months. The Botswana National ART Programme also recommends CPT for HIV-positive patients with CD4 counts of less than 200 cells/µl; patients on ART with a detectable viral load; patients on ART with immunological and or virological failure and HIV-positive patients co-infected with TB. Though these
recommendations are in place, a sizeable proportion (27.9%) of the study population did not have a documented record of having received ART, CPT or history of receiving IPT.

5.5 Limitations of the study

As with all retrospective studies, this study had some limitations. Study findings may be subject to bias, random error and confounding. The occurrence of bias was minimised by using a standardised data abstraction form. Random error was minimised by including all 1718 TB cases that met the inclusion criteria in the study. The effect of confounding was minimised by using multivariate regression analysis including variables such as age, gender, HIV status, and treatment group and treatment classification. Other factors that may affect mortality such as co-morbidity, CD4 count if HIV-positive, weight, occupation and smear results were not included in the regression analysis due to non-availability (not documented) or inconsistencies of the variables. The routine data that were recorded in the ETR did not give information on the level of education, type of housing and economic status to allow for analysis of the effect of these variables on mortality. Some of the patients on treatment during the study period did not have a documented HIV status while on treatment. The exclusion of defaulters is another limitation in this study as some of the defaulters might have died and their death not reported to the facility to update the ETR. Thus, the reported mortality among the TB patients in the study period may be higher that was is reported.

5.6 Summary

This chapter presented the discussion of the important findings of this study in relation to the study objectives. The predictors of death identified in the study include: prior history of TB infection, EPTB, HIV status, HIV-related intervention and advancing age. Gender was not a predictor of death in this study. The independent predictors of time to death among the study population were HIV-related interventions (ART and CPT). Patients had the highest risk of dying in the first two months of TB treatment. Some other interesting findings in this study include the association of EPTB with female gender, the high proportion of missing smear results, and no documentation of HIV status and HIV related interventions among the patient on TB treatment. Finally, some of the limitations of this study were discussed. The next Chapter will present the recommendations and the conclusion of the study.
CHAPTER 6
RECOMMENDATIONS AND CONCLUSION

6.1 Introduction

The previous chapter focused on the discussion of the important findings of the study. Notable findings of this study are the positive association between advancing ages, EPTB, HIV status, HIV-related intervention among TB-HIV co-infected patients, and a prior history of TB with mortality while on TB treatment. Most of the deaths in the study occurred during the intensive phase of TB treatment with all HIV co-infected cases dying during the first two months of treatment. Another notable finding is the high proportion of patients without a smear result at the beginning of TB treatment, during treatment and at the completion of treatment. This chapter presents the recommendations and conclusions of this study. The proposed recommendations will address the key findings reported in chapters four and five.

6.2 Recommendations

Based on the interesting findings and observations made while conducting this study and literature reviews, the following recommendations are proposed-

Completeness of ETR

Many important socio-demographic and clinical patient variables such as type of accommodation, type of occupation, level of education, smoking and tobacco use, patient’s weight, HIV status, HIV-related intervention, CD4 count, co-morbidity are not routinely collected in a lot of TB records. These variables are important in making decisions during TB care and management. These socio-demographic and clinical variables are important for monitoring and evaluating the TB programme as well as for research purposes. The incompleteness of the ETR makes it difficult to fully characterise study participants and analyse the impact of these variable on TB mortality. It is therefore recommended that data quality management measures be put in place to ensure that the ETR is complete and kept updated.

TB Smear result

A large proportion of the patients on treatment did not have smear results at the start of TB treatment, during treatment and at the completion of treatment. The non-availability of smear
results at the start of TB treatment implies that smear microscopy was not always used in TB diagnoses at the clinics in Francistown. Smear results are critical for TB diagnosis, monitoring the progress and success of TB treatment, and management of TB patients. The District Health Management Team (DHMT) needs to address the challenge with TB smear microscopy at the clinics.

**HIV status, HIV-related interventions and level of compliance to treatment guidelines**

Due to the high prevalence of HIV in this study and the study finding of the protective effect of ART, CPT and IPT among TB/HIV co-infected patients, it is recommended that all patients on TB treatment should have their HIV status documented; all HIV-positive patients should be initiated on ART as soon as possible and also be started on CPT. Strengthening of the TB/HIV services integration in the clinics is highly recommended. Compliance to treatment guidelines in terms of TB diagnosis and TB case management is crucial to the success of the Botswanan National Tuberculosis Programme. Studies are required to find out the level of compliance to TB treatment guidelines and shed light on the pattern of TB diagnoses at the clinics.

**Documentation of co-morbidity among TB patients**

Currently, only HIV as a co-morbidity is routinely documented in the patient’s TB record. The documentation of any other co-morbidities apart from HIV should be made routinely as different co-morbidities have been shown to predict mortality while on TB treatment.

**Need to establish cure status of patient after completion of TB treatment.**

The treatment completion rate does not necessarily equal to treatment cure rate. The cure rate is an important index in evaluating the effectiveness of the TB programme. If TB patients are treated properly and are cured, TB patients with previous history of TB in the system will be reduced with the potential to reduce the associated TB mortality rate. In light of the findings from this study, interventions to reduce defaulting TB treatment should be put in place at the clinics. All patients with a previous history of treatment default should be monitored closely to prevent defaulting on retreatment and the development of drug resistance.

**6.3 Conclusion**

Among the 1718 adult patients treated for TB in Francistown health facilities from January 2010 to November 2016 that were included in this study, a total of 161 (9.37%) died while on
treatment. The predictors of death identified in the study include: prior history of TB infection, EPTB, HIV status, HIV-related intervention and advancing age. Gender was not a predictor of death in this study. The overall median time to death in the study was 52 days. Patients with no history of TB were likely to die within five months of being on TB treatment. All TB patients with HIV co-infection who did not receive ART and or CPT died during the intensive phase of TB treatment (first two months). More than half of the deaths recorded in this study occurred during the intensive phase of TB treatment. After adjusting for gender, age, treatment classification, treatment group, and HIV status - lack of HIV-related interventions (ART and CPT) during TB treatment was a significant independent predictor of time to death among patients with TB/HIV co-infection in this study. Thus, antiretroviral therapy and CPT were found to be protective of death in the study among TB/HIV co-infected persons.

Some other interesting findings in this study include the association of EPTB with female gender, the high proportion of missing smear results and non-documentation of HIV status, and HIV related interventions among patients on TB treatment.

The association between HIV and risk of mortality among TB/HIV co-infected patients was clearly demonstrated in this study. This finding implies that patients diagnosed with TB in these health facilities must have their HIV status established and appropriate HIV-related therapy administered to minimise the risk of dying while on treatment. Thus it is imperative in the light of this finding and many other reports to continue to strengthen the linkage between HIV and TB care and services. All patients seen at the HIV clinics should be screened for any underlying TB at every clinic consultation.
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Appendices

Appendix 1: University of the Western Cape Senate Research Committee Ethics approval

![Image of Appendix 1](image-url)
Appendix 2: Botswana Ministry of Health Ethics approval

REFERENCE NO: HPDME 13/18/1 X (408) 14 March 2016

Health Research and Development Division

Notification of IRB Review: New application

Mr. Kunle Dare
P O Box 503052
Gaborone
Botswana

Protocol Title: PREDICTORS OF DEATH AMONG TUBERCULOSIS PATIENTS WHILE ON TREATMENT IN LOCAL HEALTH FACILITIES IN FRANCISTOWN

HRU Approval Date: 14 March 2016
HRU Expiration Date: 13 March 2017
HRU Review Type: HRU reviewed
HRU Review Determination: Approved
Risk Determination: Minimal risk

Dear Mr. Dare

Thank you for submitting new application for the above referenced protocol. The permission is granted to conduct the study.

This permit does not however give you authority to collect data from the selected sites without prior approval from the management. Consent from the identified individuals should be obtained at all times.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal must be submitted to the Health Research and Development Division in the Ministry of Health for consideration and approval.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research, Ministry of Health within 3 months of completion of the study. Approval is for academic fulfillment only. Copies should also be submitted to all other relevant authorities.

Continuing Review
In order to continue work on this study (including data analysis) beyond the expiry date, submit a Continuing Review Form for Approval at least three (3) months prior to the protocol’s expiration date. The Continuing Review Form can be obtained from the Health Research Division Office (HRDD), Office No. 7A.7 or Ministry of Health website: www.moh.gov.bw or can be requested
via e-mail from Mr. Kgomotso Motlhanka, e-mail address: kgmolthanka@gov.bw. As a courtesy, the HRDD will send you a reminder email about eight (8) weeks before the lapse date, but failure to receive it does not affect your responsibility to submit a timely Continuing Report form.

**Amendments**

During the approval period, if you propose any change to the protocol such as its funding source, recruiting materials, or consent documents, you must seek HRDC approval before implementing it. Please summarize the proposed change and the rationale for it in the amendment form available from the Health Research Division Office (HRDD), Office No. 7A 7 or Ministry of Health website: www.moh.gov.bw or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: kgmolthanka@gov.bw. In addition submit three copies of an updated version of your original protocol application showing all proposed changes in bold or “track changes”.

**Reporting**

Other events which must be reported promptly in writing to the HRDC include:

- Suspension or termination of the protocol by you or the grantor
- Unexpected problems involving risk to subjects or others
- Adverse events, including unanticipated or anticipated but severe physical harm to subjects.

If you have any questions please do not hesitate to contact Mr. P. Khulumani at phkulumani@gov.bw, Tel: +267-3914467 or Lemphi Moremi at lamoremi@gov.bw or Tel: +267-3632754. Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours faithfully

P. Khulumani
For/Permanent Secretary

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**Vision:** A Model of Excellence in Quality Health Services.

**Values:** Botsh, Equality, Timeliness, Customer Focus, Teamwork.
3rd November 2015

Centre for Disease Control and Prevention
TB/HIV Research
P/Bag P410
Francistown

Dear Mr. Kule Dare

RE: APPROVAL TO USE DISTRICT TUBERCULOSIS RECORDS

This serves to inform you that you have been granted permission to use our District Tuberculosis records to carry out a research study in Tuberculosis (TB) focusing on the predictors of death in TB patients in Francistown health facilities as per your request.

Please feel free to contact our TB office at any time for assistance.

Yours faithfully

Doctor Mokale
District TB Coordinator
72625872/ 2413808
Appendix 4: Data abstraction form

DATA ABSTRACTION FORM

1. Patient study number: 

2. Age: (years) 3. Sex: Male  Female

3. Clinic:__________________________

4. Occupation:
   Student  Health care worker  Miner/Ex  Other

5. Patient weight:
   Initiation phase: Month 1: ___ kg  Month 2: ___ kg
   Continuation phase: Month 3: ___ kg  Month 4: ___ kg
   Month 5: ___ kg  Month 6: ___ kg

6. Treatment classification
   Pulmonary  Extra-pulmonary

7. Treatment group
   New  Retreatment:
   Failure  Default  Relapse  Other

8. Sputum examination for AFB: Result (*P/N)
   Month 0:  Month 2:  Month 3:  Month 6:  Month 8:

9. HIV Status and interventions
   HIV: Positive  Negative
   *ART: Yes  No
   *IPT: Yes  No
   *CPT: Yes  No

10. Treatment Outcome: Died  Alive

Key:
Failure: a patient who is started on a retreatment regimen after having failed previous treatment.
Default: a patient who return to treatment, positive bacteriologically, following interruption of treatment for 2 months or more with smear or culture positive TB.
Relapse: a patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with sputum smear positive or culture positive TB.