DETERMINANTS OF DELAY IN THE DIAGNOSIS AND TREATMENT OF SUSPECTED TUBERCULOSIS BY HIV STATUS IN SOUTH AFRICA

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DECLARATION

I declare that this research report that I submit in partial fulfilment of the degree, Masters in Science in Epidemiology and Biostatistics at the School of Public Health at the University of Witwatersrand, Johannesburg is my independent work. This research report has not been submitted previously to any institution for examination or degree purposes.

Victor Kanje

Date: 22nd June 2017

DEDICATION

I dedicate this work to my wife, Georgina, and my son, Kendrick. Without the support of my wife, this research report would not have been possible. I want to thank her for unrelenting support and understanding and for looking after my son so that I can work on my research report. My Son, Kendrick, You inspire me to work extra hard and achieve more in life.

ABSTRACT

Introduction

Delays in diagnosing and treating tuberculosis increase the risk of transmission, morbidity and mortality especially in low socio-economic settings with high HIV and TB rates. The aim of this study was to determine factors associated with the delay in the diagnosis and treatment of suspected TB by HIV status in hospitalised patients in South Africa.

Methods

This study was a secondary analysis of data from a three centre prospective cohort of inpatients recruited between 2006 and 2009 that were clinically diagnosed with active TB on admission.

Results

Data from 1018 patients (67% female) of a median age of 36 years (IQR: 30-44) with known HIV status were analysed: 875 (86%) positive and 143 (14%) negative. HIV positive patients had significantly longer median total delays relative to the negative (39 days, IQR: 28-74 vs. 32 days, IQR: 21-56; $p<0.02$). Unemployment, seeking prior treatment and use of cotrimoxazole predicted total delay in the HIV positive patients.

Conclusion

Patient delay is high in HIV positive patients compared to the HIV negative. Public health interventions targeting earlier diagnosis of TB disease in HIV positive patients should be enhanced.

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AIDS	:	Acquired immunodeficiency syndrome
AOR	:	Adjusted Odds Ratio
BMI	:	Body Mass Index
CI	:	Confidence interval
DOTS	:	Directly Observed Therapy
ELISA	:	Enzyme-Linked Immunosorbent Assay
GPs	:	General Practitioners
HIV	:	Human Immunodeficiency Virus
IQR	:	Interquartile Range
Mtb	:	Mycobacterium Tuberculosis
MDR-TB	:	Multidrug-resistant tuberculosis
OR	:	Odds Ratio
PHRU	:	Perinatal HIV Research Unit
SES	:	Socioeconomic Status
SOWETO	:	South Western Townships
TB	:	Tuberculosis
Wits HREC	:	University of the Witwatersrand, Human Research Ethics Committee
WHO	:	World Health Organisation

CHAPTER ONE: INTRODUCTION

The chapter gives an overview of the burden of tuberculosis (TB) and its significance in public health. It also discusses the double burden of TB and HIV in sub-Saharan Africa and South Africa in particular. This chapter further reviews the literature on determinants of delay in diagnosis and treatment of TB. The problem statement, justification for conducting the study and research objectives are also included.

1.1 Background

Tuberculosis (TB) is one of the most common infectious diseases that cause morbidity and mortality worldwide (1). The World Health Organisation (WHO) ranks TB alongside HIV as a leading cause of death among infectious diseases globally (2). In 2015, approximately 10.4 million people worldwide were infected with TB (5.9 million men, 3.5 million women and 1.0 million children) and 11 percent of all new TB cases were HIV positive (2). Although there has been a 42 percent decrease in the prevalence of TB globally from 1990 to 2015, the number of cases (174 cases per 100,000 populations as of the year 2014) is still unacceptably high (2). Furthermore, there has not been any significant decrease in prevalence in developing countries especially in sub-Saharan Africa where the double burden of TB and HIV is high (1). The WHO Global Tuberculosis Report of the year 2016 estimated that the number of deaths due to TB was 1.4 million in 2015 and an additional 0.4 million deaths occurred among TB and HIV co-infected patients (2). Over 95 percent of these deaths took place in low and middle-income countries. These unacceptably high TB mortality rates can be controlled with a timely diagnosis and correct treatment (1).

In sub-Saharan Africa, South Africa has the highest burden of HIV and TB. A South African household survey approximated that 18.8 percent of the reproductive age population (15 to 49 years) are HIV positive (3). The incidence of TB in South Africa is among the highest in the world at 834 new cases per 100,000 people (2). The profile of HIV epidemic in South Africa is also among the highest in the world. In the year 2012, there was an estimated 469,000 new HIV infections, and about 6.4 million people were living with HIV(3). Furthermore, South Africa's HIV and TB co-infection rates are highest in the world

with an estimated incidence of 473 new cases per 100,000 people (2). Such elevated levels of TB and HIV co-infection substantiates the fact that HIV/AIDS drives the TB epidemic in South Africa and it also explains why TB is the leading cause of death among people infected with HIV in the country (4).

In South Africa, the population group that is highly affected by TB and which constitutes 88 percent of all TB cases are people aged 30 to 39 years, living in townships and informal settlements (5). It may, therefore, imply that TB is a disease that affects people in poverty stricken environments as most of the township and informal settlement settings are characterised by overcrowding and low socio-economic status, all of which provide a favourable environment for TB infection and disease (5).

Gauteng is one of the nine provinces in South Africa and home to South Western Townships (SOWETO). Soweto is one of the largest and most populated townships characterised by several informal settlements. The prevalence of HIV in Gauteng province is 12.4 percent (3). Program data from the South African Department of Health estimates that the province has the third-highest number of people with TB in the country with an estimated TB incidence of 376 per 100,000 people and around 30 to 40 percent of TB patients are infected with HIV (Department of Health, unpublished data). It has been established that reactivation of latent TB infection plays a significant role in the escalating TB epidemic in South Africa, as even populations with extremely effective Directly Observed Therapy (DOT) programs such as miners experience unprecedented increases in TB morbidity (6).

1.2 Aetiology of tuberculosis

The bacillus, *Mycobacterium tuberculosis* (Mtb), causes TB and the source of Mtb infection is commonly individuals with untreated pulmonary TB. Transmission to susceptible persons occurs when they have been exposed to droplet nuclei containing viable organisms that have been aerosolized from an infectious source (1). Most of the individuals infected with Mtb do not show symptoms. However, in a minority of infected people, the initial infection may progress to active clinical disease within two years (7). Although reactivation of tuberculosis occurs years after the initial infection in a small

proportion of patients, the majority of persons infected with Mtb never develop clinical disease (8).

Early detection of TB disease is critical in alleviating transmission and prolonging of the disease in an individual. Furthermore, it cuts down on time between onset of first symptoms, diagnosis and treatment (9). Contagiousness of TB increases as an infected person delays seeking treatment (10) thus exposing those sharing the same surrounding with the patient to TB.

Many authors have documented that failure of TB control mechanisms are a contributing factor to the delay in diagnosis and treatment of TB (9, 10). A longitudinal cohort study conducted in Guinea-Bissau showed that delayed diagnosis and treatment results in escalating the severity of the disease, mortality and transmission (9). There is an increased risk of TB transmission if the time between the onset of first symptoms of the disease, diagnosis and treatment is long (9). A cross-sectional study conducted in Ethiopia demonstrated that delayed treatment results in the likelihood of bacterial resistance which leads to an increased mortality risk and consequently the success of the treatment decrease (11). A study conducted in Iran further documented that bacterial resistance which resulted in the occurrence of multidrug-resistant tuberculosis (MDR-TB) made TB control to be more challenging and this vicious cycle continues (12).

Studies conducted in most developing countries have shown that delays in diagnosis and treatment of TB occur in both high and low TB prevalence settings like sub-Saharan African countries and Croatia respectively (13-17). Different authors have widely recommended that understanding the factors that lead to the delay in diagnosis and treatment is one of the key steps to be considered when designing and implementing a TB control programme (18, 19).

1.3 Problem statement

Globally, most authors have attributed delays in TB diagnosis and treatment to the female gender, HIV infection, old age, alcoholism, low social-economic status, lack of knowledge about TB symptoms among both patients and health workers and prior unspecific

treatment for TB (10, 13, 20-22). Studies conducted in Sub-Saharan Africa where poverty and the burden of HIV are high have found similar results. However, the Sub-Saharan studies have further found that unemployment, seeking prior treatment, perceived stigma and crowding index determine delays in TB diagnosis and treatment (14, 17, 23, 24). In developed countries with a low burden of TB, low index of TB suspicion by patients and health care workers continue to influence the delays in TB diagnosis and treatment (1). In Sub-Saharan African countries, persistent poverty and underdevelopment which affects access to proper TB diagnostic and treatment services remain a key factor which influences the delays (18, 25).

Delay in the diagnosis and treatment of TB is often classified into patient, health system and total (sum of patient and health) delays and the determinants of all these classes of delay have been widely assessed (13, 19, 21, 24). Although such determinants have been widely reported, there is limited literature comparing them by HIV status in hospitalised patients in South Africa where the burden of TB and HIV is high.

1.4 Justification for study

There is a need for evidence-based interventions that would result in effective TB diagnostic and treatment for both HIV positive and negative patients to reduce diagnostic delay and expedite TB treatment. However, there is limited evidence which demonstrates whether determinants of delay in TB diagnosis and treatment in HIV-infected cases are different from those who are HIV negative. In South Africa, TB and HIV co-infection rates are high compared to other countries in sub-Saharan Africa (5).Understanding the determinants of delay by HIV status in such a setting is critical to effective TB programming. This study, therefore, addressed these knowledge gaps and the results will inform the policies, strategies and targeted interventions that could improve early detection and treatment of TB among HIV positive and HIV negative patients. Such interventions would ultimately reduce TB-related morbidity and mortality.

1.5 Literature review

1.5.1 Definition of delay

Several authors have classified delay into patient, health care system and total delay (10, 14, 24). A recent study conducted in Ghana defined patient delay as the duration of time between the onset of the first TB symptoms and first contact with public health services (23). Studies conducted in South Africa and Italy used similar definition (20, 24). Many authors agree that health system delay is the number of days between making contact with a health facility and initiation of anti-tuberculosis treatment and that the sum of patient and health system delay is the total delay (8, 10, 24, 26).

Many quantitative studies conducted across the world have measured delay as a binary outcome where a particular cut-off point is set to describe prolonged delay (18, 24). The definition of prolonged delay varies from one study to another depending on the study setting. The period of approximately a month or more from initial symptoms to seeking any medical care has been used to characterise prolonged patient delay, while a period of 15 days from visiting a medical facility to initiation of treatment has been used to describe prolonged health system delay (9, 13, 18, 24). A study conducted in South Africa defined prolonged patient delay as having symptoms for at least 28 days before seeking any medical care while prolonged health system delay was defined as starting anti-tuberculosis treatment at least seven days after first reporting to any medical facility (24).Other authors have used the median value of the observed data as a cut-off for prolonged delay (27). No standard period defines total delay from the onset of symptoms to the commencement of TB treatment. However, some authors have suggested that this period should not be more than one month (28) while others have argued that the period can be as long as two months (29).

1.5.2 Distribution of delay

Research from Zimbabwe, a developing country with a high burden of HIV and TB, found that the median patient delay was 28 days (17). Similar results emerged from a retrospective cohort study conducted in Norway, a developed country with low burden

HIV and TB (30). However, different distribution of patient delay, median 59 days, has been observed in a recent study conducted in Ghana comprising of suspected TB patients who were 15 years and older and were admitted between 1st June 2013 and 31st May 2014 in Hohoe Municipality (23). Considerable differences also emerged from a study consisting of 104 patients admitted in South Africa, a setting with high HIV and TB burden, in 2008 where the median patient delay was 14 days (31). It may, however, be difficult to ascertain whether the differences in the distribution of patient delay from different study settings was due to bias or due to actual observed differences across the study settings. This is because cross-sectional and retrospective cohort studies are more prone to recall bias where the patients may not correctly remember the date during which the first symptoms suggestive of TB infection occurred.

The distribution of health system delay varies extensively in different settings. For instance, a study conducted in seven Croatian counties between April and December 2006 among adults of 15 years of age and above found that the median health system delay was 15 days (16). On the contrary, a recent study conducted in Zimbabwe found that the median health system delay was 2 days (IQR: 1-5) (17). A cross-sectional study conducted in 10 sub-districts of Bangladesh whose aim was to examine the gender variations in patient and health system delay among TB patients found the median health system delay to be one day for both males and females (32). Different results were obtained from two cross-sectional studies conducted in urban settings of high HIV and TB burden countries Malawi and Mozambique were the median health system delay was 59 days (IQR: 26–108) and 62 days (IQR: 37–120) respectively(25, 33). Researchers have associated health system delay to the index of TB suspicion among health workers (10, 18, 33). Differences in levels of knowledge about signs and symptoms of TB could, therefore, be the reason why there is a high variation in the distribution of health system delay across different studies.

Previous studies have shown vast differences in the total delay across several settings which range from 25 days to 185 days and the main reason for such differences has been attributed to variability in demographic factors among others (8, 9, 11, 12)**.** A prospective cohort study conducted in Amhara Region of Ethiopia from October 2013 to May 2015 among newly diagnosed PTB patients who were 15 years of age and above found that the

median total delay was 60 days(34). A study that was meant to describe the risk factors for treatment delay and the effect of delay on the severity of tuberculosis (TB) in a prospectively followed TB cohort at the Bandim health project in Guinea-Bissau found that the median total delay was 85 days (9). A systematic review whose aim was to systematically review Indian literature on delays in TB diagnosis and treatment obtained a median total delay of 55 days (IQR: 47–62) (19).

1.5.3 Determinants of delay

Researchers from different countries have demonstrated that delays in treatment and diagnosis of TB are affected by a wide range of demographic and diagnostic factors among others (8-12, 18). According to these studies, these predictors of delay have appeared to differ sometimes based on the research setting. A systematic review conducted elsewhere indicated that the most common factors include, old age, low level of education, little public awareness of TB, long distance to health facilities, male gender, the first visit by a physician not familiar with the National TB control programme, rural residence and HIV infection(10). Furthermore, researchers have studied other characteristics that affect delay in diagnosis and treatment of TB including socio-economic status, crowding index, Body Mass Index (BMI), use of medication that suppress TB infection e.g. cotrimoxazole, use of alcohol and cigarettes and employment status(18, 23, 24, 33). These characteristics have shown to have an association with a delay in other settings, and they have shown no relationship in others.

1.5.3.1 Prolonged patient delay

Studies conducted in developed countries have indicated that the elderly (> 65 years) are more likely to experience prolonged patient delay than the younger patients while sex, smoking and alcohol use are not associated with prolonged patient delay (30, 35). Some studies conducted in developing countries agree with the notion that old age is related to prolonged patient delay and that sex is not associated with delay (14, 23). Conflicting revelations concerning gender were found in a study conducted among a high HIV population in South Africa where male sex was independently associated with longer patient delay (31). A systematic review that was done in sub-Saharan African countries

with a high burden of TB and HIV further demonstrated that patients who sought treatment elsewhere before TB treatment had a longer patient delay than those who never seek treatment elsewhere (14). A study conducted in Ghana demonstrated that patients who are employed have higher odds of prolonged patient delay (OR: 2.87; 95 % CI: 1.02–8.09; P<0.046) when compared to the unemployed ones (23). Several studies conducted in both developed and developing countries have discovered that body mass index, HIV infection and socio-economic status do not significantly predict prolonged patient delay (8, 13). A study conducted in Thailand found that being HIV positive was associated with reduced odds of prolonged patient delay(36) while Storla et al in a systematic review found the direct opposite where HIV infection was associated with increased odds of prolonged patient delay (10). The Thailand study was conducted in a high TB and HIV epidemic region which could mean that there was increased level of awareness about HIV and TB co-infection hence the patients had to seek medical care in time. On the other hand, the systematic review might have included some studies that were conducted in low HIV and TB-endemic region, and people's suspicion of TB was low since it was not a common condition within their settings and awareness was low. Storla's results can, however, be explained based on revelations in urban India where fear of stigma and discrimination associated with HIV infection led to patients delay in seeking medical care (37).

1.5.3.2 Prolonged health system delay

Although some studies have not found any association between HIV status and prolonged health system delay (10, 31), studies conducted in Northwest Ethiopia and Thailand revealed that HIV-positive patients were less likely to have increased health systems delay compared to HIV-negative patients (8, 36). According to the study conducted in Thailand, patients with HIV infection present more severe symptoms suggestive of TB disease than those with HIV negative making it easier and quicker for health care workers to suspect TB and initiate them on treatment than those that are negative (36). The Northwest Ethiopian study gave a different explanation by indicating that health care workers have a high index of TB suspicion among HIV positive patients than HIV negative ones which accelerates diagnosis of TB among self-reported patients unlike those without HIV in areas were high TB and HIV co-infection exist (8). Furthermore, in such settings there

could have been increased awareness of TB among health care workers resulting in reduced period to diagnose and initiate TB treatment among patients.

Previous research has also revealed that patients who had sought treatment elsewhere had higher odds of non-parametric health system delay than those who never sought treatment elsewhere (13, 25, 31). In additional to being in agreement with such findings, a study conducted in Khuzestan province in Iran demonstrated that smoking results in increased odds of prolonged health system delay (13). However, several findings from studies carried out in different settings have shown that smoking is not associated with prolonged health system delay (14, 30, 33). There is no clarity in the way the frequency or extent of smoking was defined in the Khuzestan province study, and this could be the source of variation with other studies that found conflicting results since most considered those who have ever smoked regardless of whether they stopped or not.

In other studies, researchers have established an association between employment status and prolonged health system delay in which employed patients experienced shorter health delay than the unemployed (31).

1.5.3.3 Prolonged total delay

Research has demonstrated that the main problem in delay appears to be a vicious cycle of frequent visits at the same healthcare level, resulting in nonspecific antibiotic treatment and failure to access specialised TB services (9, 13, 38). Studies have associated the level of socioeconomic status to health seeking behaviour of individuals. For instance, studies conducted in Tanzania, Brazil and Hong Kong showed that people who were of low socioeconomic status were more likely to experience delays in diagnosis and treatment of TB (39-41). A related discovery was made in studies conducted in Rwanda and Gambia which showed that prolonged total delays were prevalent in rural residence which other authors have also associated with low socioeconomic status (42, 43). Much as other studies have found no association between gender, smoking and alcohol intake and delays in diagnosis and treatment of TB (39, 44), but studies conducted elsewhere have shown that female sex, alcohol consumption and smoking are associated with prolonged total delay(13, 24).

In most study settings, health system delay has been a major contributor to prolonged total delay than patient delay. A comparison of patient delay and health system delay in South Africa's rural Northern Province found the health system delay to be a much larger problem than patient delay (45). Several studies agree with this notion and further demonstrated that low index of suspicion for diagnosing TB among health care providers is the leading cause of the problem (13, 15, 21). Amongst the factors discussed in this review, some researchers have isolated lack of public awareness of signs and symptoms of TB among health workers and the general population as the most important factor (21). Research conducted in Ethiopia also showed that limited knowledge about the signs and symptoms of TB caused a delay in referring patients to facilities, as well as a delay in diagnosing TB at the health facility (15). A comparative study of knowledge about tuberculosis in two cities with different tuberculosis epidemiological index in Khuzestan revealed that awareness about the disease in the general population and some health professionals is low (13).

1.6 Research qquestion

What are the determinants of delay in the diagnosis and treatment of suspected TB among HIV positive patients compared to HIV negative patients in three hospitals (Chris Hani Baragwanath, Selby Park and Tshepong hospital) in South Africa between 2006 and 2009?

1.7 Aim of study

To compare the determinants of delay in diagnosis and treatment of suspected TB among HIV positive and HIV negative patients in three hospitals (Chris Hani Baragwanath, Selby Park and Tshepong hospital) in South Africa between 2006 and 2009

1.8 Objectives of study

1. To identify demographic and clinical differences between HIV positive and negative TB patients.

2. To determine the distribution of patient, health care system and total delay in days stratified by HIV status.
3. To determine factors associated with prolonged patient, health care system and total delays in diagnosis and treatment of suspected TB by HIV status.

1.9 Report structure

This report has five chapters; the introduction, methods, results, discussion and conclusion. The introduction gives an overview of the dual burden of HIV and tuberculosis (TB) and its significance in public health. It also reviews the literature on determinants of delay in diagnosis and treatment of TB and provides the rationale as well as objectives for the research. The methods chapter describes the study design, study population, data management, variables, statistical methods and data analysis as well as ethical considerations for the study. The results chapter provides details of the research findings after analysing data. The discussion chapter reviews the findings of the study in relation to available literature and provides possible deduce explanations to observed results. The conclusion provides recommendations to public health practice and policy based on the results. It also discusses the strength and limitations of the study.

CHAPTER TWO: METHODS

This chapter presents a description of the study design, study population, data management, variables, statistical methods and data analysis as well as ethical considerations for the study.

2.1 Study design

This was a retrospective cohort study which utilised secondary data from a three- centre prospective cohort of inpatients who were clinically diagnosed during the first 24 hours of admission with active TB in three hospitals (Chris Hani Baragwanath Academic Hospital and Selby Park Hospital, both in Gauteng Province, and Tshepong Hospital in North West Province) in South Africa between August, 2006 and October, 2009. The primary study aimed at determining factors associated with mortality in hospitalised TB patients with active TB irrespective of their HIV status. Data for the primary study was corrected using hospital records and predesigned questionnaires which were administered to the patients.

2.2 Study population and sampling

The study based on data from a three-centre prospective cohort of inpatients clinically diagnosed with active TB in South Africa between 2006 and 2009. The participants in the parent study were adults who were at least 18 years of age and TB had to be included in the differential diagnosis during the first 24 hours of admission. Both HIV positive and negative patients formed part of the study population, and the total number of participants recruited was 1018 people. The analysis included all enrolled participants with known HIV status.

2.3 Data management

The data for the secondary analysis was obtained from the Datafax system at the Perinatal HIV Research Unit (PHRU) of Chris Han Baragwanath hospital. The data were

imported into STATA version 13.1 (Stata Corporation, College Station, Texas, USA) for statistical analysis. The database was monitored and cleaned on an ongoing basis with quality assurance processes in place. Before analysing, validity checks were done to ensure completeness and to identify transposition, copying, consistency and range errors. This was done by performing frequencies and cross tabulations. Discrepancies were resolved by comparing the database with the hard copy of the forms. The database was then corrected accordingly. The variables of interest were recoded and categorised as necessary.

2.4 Measurement of variables

All variables were defined before the data were analysed.

2.4.1 Exposure

HIV status: The variable was measured as a binary variable and was defined as either HIV positive or HIV negative. The information was obtained from the medical history, and it was confirmed by results of the laboratory examination of the patient's blood where either two rapid HIV test or Enzyme-Linked Immunosorbent Assay (ELISA) test was conducted. Conclusive evidence of one's HIV status was ascertained from the laboratory examination results. Missing information from the laboratory results was replaced by information from the medical history.

2.4.2 Potential confounders and covariates

- **Age:** This was calculated from the date of birth to the date of admission. Age was self-reported and verified through an identity document. Age was categorised because it was not normally distributed for both HIV positive and HIV negative patients. The age groups that were used were chosen based on the age limit on inclusion criteria and also in line with what is used by most authors:

  18 – 29 years

  30 – 44 years

  >45 years

- **Sex**: This binary variable was self-reported and was categorised as follows:

  Male

  Female

- **Socio-economic status (SES)**: Factor analysis using a list of variables describing a variety of assets and other possessions of the participant were used to create three categories of the SES variable as follows:

  Lower class

  Middle

  Upper middle class

  These groups were chosen because the area where the most participants come from (i.e. SOWETO) is of low socioeconomic profile and most people in the area are either in the poor or middle class.

- **Type of house**: This variable was binary, and was recoded from a five-category variable which included brick house, shack, hostel, garage and other. The recoded variable was categorised as ‘brick house' and ‘other' where all groups apart from brick house formed part of the ‘other' category.

- **Numbers of rooms in the house**: This was measured as a discrete variable, and for each patient, it was defined as the number of rooms in the house where people sleep.

- **Number of people in the house**: This was measured as a discrete variable, and for each patient, it was defined as the number of people living in the household.

- **Crowding Index**: This variable was generated by dividing the number of people in a household divided by the rooms in the house and was measured as a continuous variable.

- **Employment status**: This binary categorical variable was classified as either ‘employed' of ‘unemployed'. Those who were in the unemployed category had to be unemployed for more than three days a week for the past two months.

- **Smoking:** This was self-reported, and it was a binary variable with a ‘yes' or ‘no' response. The variable was defined as current smokers or those who had ever smoked.

- **Alcohol consumption**: This was self-reported, and it was a binary variable with a ‘yes' or ‘no' response. The variable was defined as those who currently drink alcohol or those who had ever drunk alcohol against those who had never consumed alcohol.

- **Admission time:** This variable was generated from the day of admission variable. The day of admission was changed to a format which indicated the day of the week during which the patient was admitted. It was then categorised as ‘weekday', for Monday to Friday, and ‘weekend' for Saturday and Sunday.

- **Body Mass Index (kg/m^2):** BMI was calculated by dividing weight (in kg) by the square of height (in meters). It was then recorded and categorised as underweight for BMI<18 kg/m^2, normal weight for BMI 18.5-24.9 kg/m^2 and overweight or obese for BMI >25 kg/m^2. The classification of the BMI variable was based on standard WHO guidelines for BMI classification.

- **Cotrimoxazole**: This was self-reported, and it was a binary variable with a ‘yes' or ‘no' response. The variable was defined as those who are currently taking Cotrimoxazole or have taken the drugs in the past week for longer than five days.

- **Sought treatment elsewhere:** This was self-reported, and it was a binary variable with a ‘yes' or ‘no' response. The variable was defined as having been admitted to another doctor, clinic or hospital because of the patient's current problem before their current admission.

- **Hospitals type:** This categorical variable was based on which Hospital the patients were admitted, and it had three groups including:

  Chris Hani Baragwanath hospital in Soweto

  Selby hospital in Johannesburg Central Business District

  Tshepong hospital in Klerksdorp

2.4.3 Outcome variables

The outcome variable was delay and it was measured on three levels of patient delay, health system delay and total delay.

- **Patient delay:** This discrete variable was defined as the number of days between onset of TB symptoms and the first contact with any health care provider. The longest duration of symptoms suggestive of TB was considered.

- **Prolonged patient delay.** This variable was measured as a binary outcome. Study subjects with a patient delay of more than 28 days were categorised as having experienced prolonged patient delay unlike those that had a patient delay of fewer than 28 days.

- **Health system delay:** It was defined as the number of days between admission and initiation of anti-tuberculosis treatment. The variable was obtained from the difference between the first day of admission to a health facility and the first day the patient was initiated on anti-tuberculosis treatment.

- **Prolonged health system delay**: This binary outcome variable was derived from the discrete health system delay variable. Patients who experienced 7 days or more in health system delay were classified into the prolonged health system delay category while those who had less than 7 days were not.

- **Total delay:** The variable was obtained from the sum of patient and health system delay.

- **Prolonged total delay**: Similarly, the prolonged total delay variable was measured as a binary outcome. Patients with 35 days or more of total delay were grouped into the prolonged total delay category while those with less than 35 days total delay were not.

2.5 Statistical methods and data analysis

2.5.1 Exploratory and descriptive analysis

Exploratory and descriptive data analysis of frequency and percentages were done for categorical variables. A test of normality was conducted for continuous variables, and since it was found that the data was not normally distributed, the median and interquartile ranges were done for the continuous variables stratified by HIV status. For categorical variables, Pearson's Chi-squared tests were conducted to assess whether the different proportions of the various categorical variables were the same in the population with HIV positive patients compared to that with HIV negative patients. For continuous variables, Mann Whitney U test (Wilcoxon Rank Sum test) was done to assess whether the population median for HIV positive patients was different compared to that with HIV negative patients.

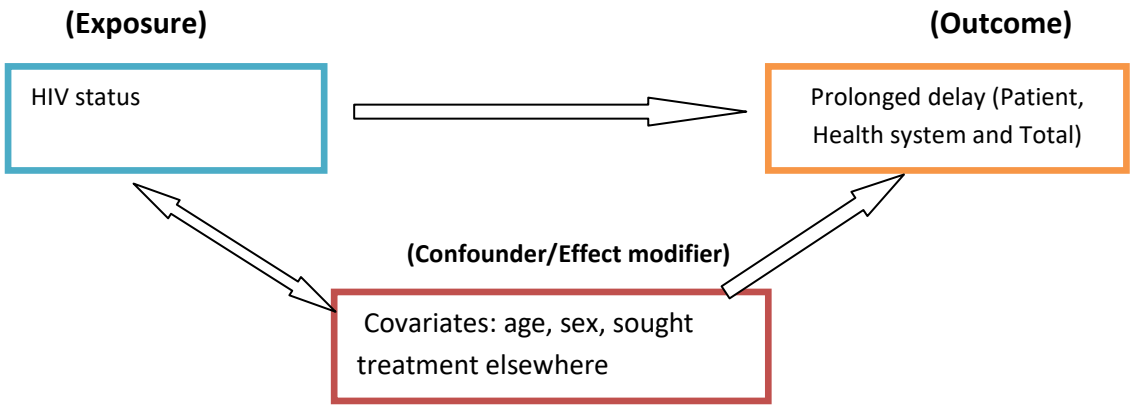
2.5.2 Calculation of Patient, Health system and Total delay

The overall frequency of all types of delay for HIV positive and HIV negative patients was calculated for some socio-demographic and clinical variables to determine the median distribution and IQR for patient, health care system and total delay. Continuous variables were assessed for normality and since they were not normally distributed non-parametric tests were used. Mann Whitney U test (Wilcoxon Rank Sum test) test was done to determine whether the median delay in the population with HIV positive patients was different compared to that with HIV negative patients.

2.5.3 Assessment of confounding and effect modification

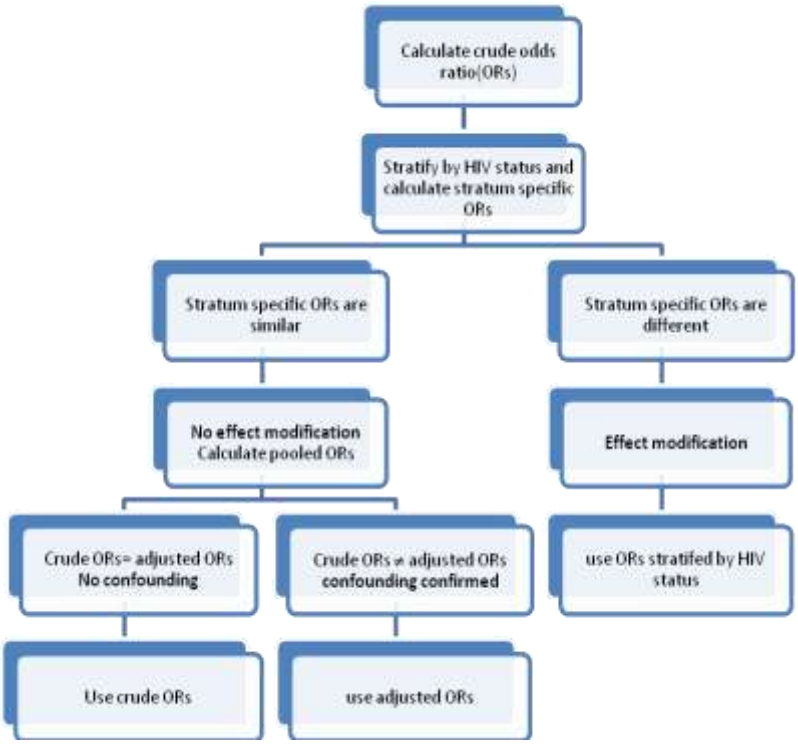
Covariates were investigated for confounding and effect modification for each type of prolonged delay. **Figure 1** shows the confounding/effect modification pathway that was investigated:

Figure 1: Diagram of confounding pathway



The assessment was done using Mantel Haenszel test of homogeneity of odds ratios and HIV status as the exposure. The crude odds ratios were calculated for prolonged delay and sought prior treatment. HIV stratum-specific odds ratios were then calculated for the same relationship. Effect modification was ascertained when the stratum specific odds ratios provided were different. For similar stratum specific estimates, pooled odds ratios were calculated. Confounding was confirmed when crude odds ratio were different from adjusted odds ratios. The algorithm for assessment of confounding and effect modification is outlined in **Figure 2**.

Figure 2: Flow chart of algorithm for confounding/effect modification assessment



2.5.4 Inferential analysis for prolonged Patient, Health system and Total delay

Logistic regression analysis was used to estimate the odds ratios (ORs) for all types of prolonged delay. Prior to fitting the regression models, several assumptions were checked that necessitates the use of the binomial logistic regression including the assumption of multicollinearity among independent variables and the linear relationship between continuous independent variables and the log odds.

Univariate logistic regression models were fitted for each type of prolonged delay to determine odds ratios, 95% confidence intervals (CIs) and associated P-values for different covariates. Significant variables with $P < 0.05$ were fitted into a multivariate model to determine predictors of all prolonged delays stratified by HIV status. Likelihood ratio tests were conducted to assess whether adding particular variables to the multivariate model helped to improve the model and those which improved the model

were retained as opposed to those which did not contribute to improving the model. This was followed by the Hosmer-Lemeshow goodness of fit test which was conducted to check model fit.

2.6 Ethical approval

Ethics approval for this study was obtained from the University of the Witwatersrand, Human Research Ethics Committee (Wits HREC) (clearance certificate number M160548). Approval for the initial study was obtained from the Wits HREC (clearance certificate number M051116). Study participants gave informed consent to participate in the primary study.

During this analysis, the information was kept anonymous. A data sharing agreement was also made between the principal investigator and the owners of the data, in this case, PHRU.

CHAPTER THREE: RESULTS

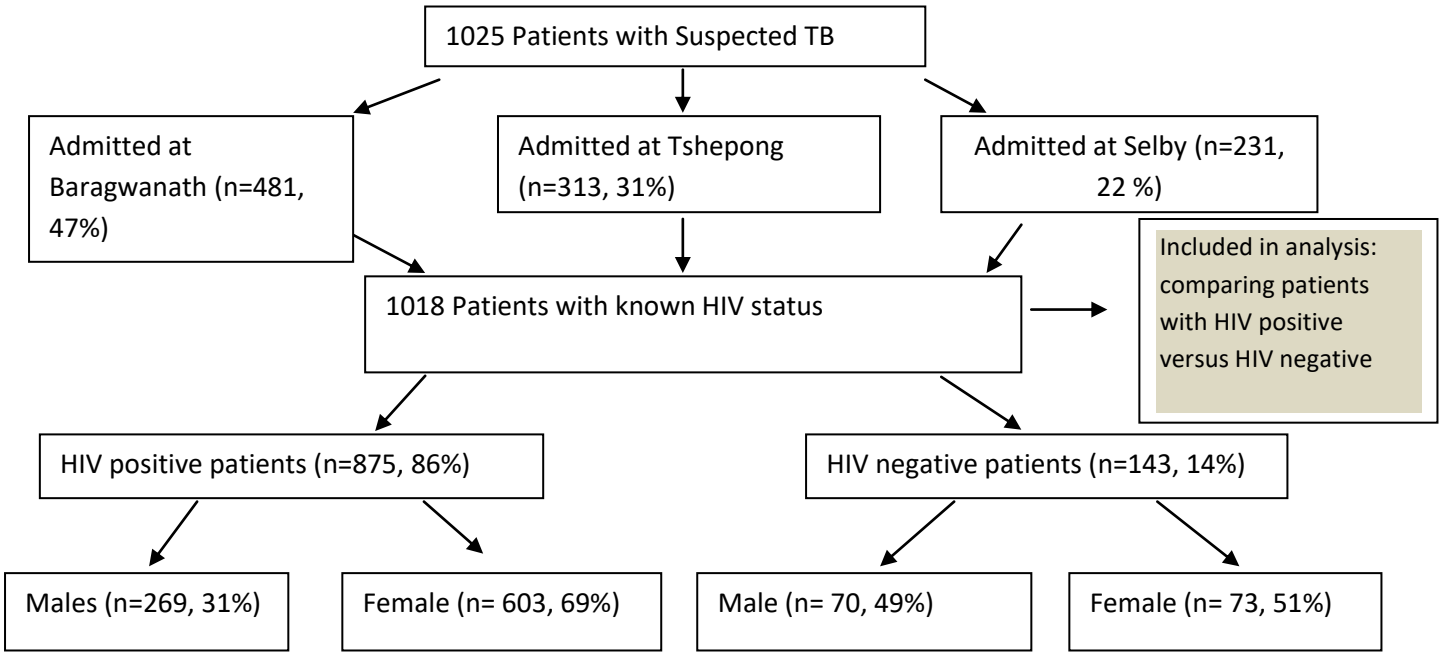
This chapter provides a detailed explanation of the study findings.

3.1 Overview

A total of 1025 suspected TB cases were identified from the primary study. Among the identified cases, 481(47%) were admitted to Baragwanath hospital, 313(31%) at Tshepong hospital and 231(22%) at Selby hospital. Out of these patients, 1018 patients had known HIV status of whom 875 (86%) were HIV positive while 143 (14%) were HIV negative. All patients were above 18 years of age, although the majority were within the age group of 30-44 (53%).

Overall, the majority of patients were females (n=679, 67%). Among the 875 HIV positive patients, 603 (69%) were females while 269 (31%) were males. Of the 143 HIV negative patients, 73 (51%) were females and 70 (49%) were males. The analysis included those patients who had known HIV status. The flow diagram in **Figure 1** shows the patients included in the analysis.

Figure 3: Flow chart of patients enrolled in the study



3.2 Socio-demographic and clinical characteristics of patients

All participants were within the age group of 18 to 83 years with an overall median age of 36 years (IQR: 30 – 44 years). A comparison of patients by HIV status indicated that the HIV positive were significantly younger (36 vs. 42 years; p<0.0001) and had a higher proportion of females (69% vs. 51%; p<0.0001) compared to the HIV negative. Furthermore, more HIV positive patients were unemployed (61% vs. 44%; p<0.0001), and had sought treatment elsewhere (53% vs. 41%; p=0.009) relative to the HIV negative.

Overall, there was almost an equal proportion of patients in different classes of socio-economic status with 336(33%) being in the upper middle class, 317(32%) in the lower middle class and 347(35%) in the poor class. There were no significant differences in the proportion of patients among different socio-economic status categories in the HIV group compared with the HIV negative group (p=0.8). Furthermore, there were no significant differences as regards to body mass index and the number of people in each house for HIV positive patients compared to HIV negative patients **(Table 1**).

Table 1: Characteristics of patients stratified by HIV status

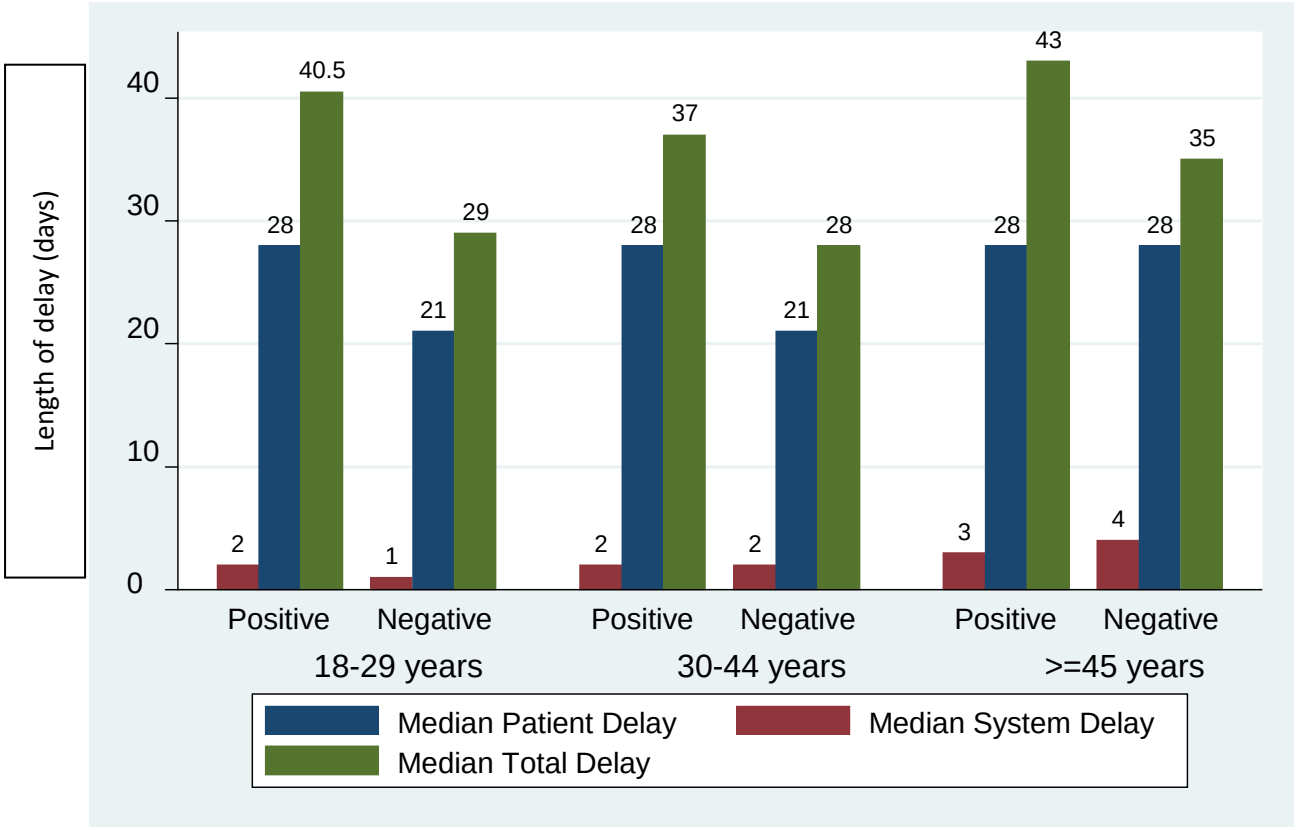
Characteristics	**Overall**	**HIV Positive**	**HIV Negative**	
	(N=1018)	**(n=875)**	**(n=143)**	
	Median (Q3-Q1) or n (%)	*Median (Q3-Q1) or n (%)*	*Median (Q3-Q1) or n (%)*	**P-Values**
Age groups (years)				
18-29 (%)	225 (22)	194 (22)	31 (22)	<0.0001
30-44 (%)	546 (54)	494 (57)	52 (36)	
> 45 (%)	244 (24)	184 (21)	60 (42)	
Median age(Q3-Q1)	36(30-44)	36(30-43)	42(31-51)	< 0.0001
Sex				
Male (%)	339 (33)	269 (31)	70 (49)	<0.0001
Female (%)	676 (67)	603 (69)	73 (51)	
Socio-economic status				
Upper middle (%)	336 (33)	292 (34)	44 (31)	0.83
Lower middle (%)	317 (32)	272 (32)	45 (32)	
Poor (%)	347 (35)	296 (34)	51(37)	
Type of house				
Brick House (%)	692 (68)	592 (68)	100 (70)	0.66

Other (%)	321 (32)	278 (32)	43 (30)	
No. of rooms in the house				
Median (Q3-Q1)	2 (2-2)	2 (2-3)	2 (1-2)	0.08
No. of People in the house				
Median (Q3-Q1)	4 (3-6)	4 (3-6)	4(3-5)	0.13
Crowding Index				
Median (Q3-Q1)	2 (1.5-3)	2 (1.5-3)	2 (1.5-3)	0.93
Employment status				
Employed (%)	418 (41)	338 (39)	80 (56)	<0.0001
Unemployed (%)	597 (59)	534 (61)	63 (44)	
Ever smoked				
Yes (%)	246 (24)	193 (22)	53 (37)	<0.0001
No (%)	770 (76)	680 (78)	90 (63)	
Ever used alcohol				
Yes (%)	291 (29)	238 (27)	53 (37)	0.02
No (%)	723 (71)	633 (73)	90 (63)	
Hospital				
Baragwanath (%)	476 (47)	398 (46)	78 (55)	<0.0001
Klerksdorp (%)	311 (30)	290 (33)	21 (14)	
Selby (%)	231 (23)	187 (21)	44 (31)	
Admission time				
Weekend (%)	98 (10)	91 (10)	7 (5)	0.04
Weekday (%)	917 (90)	781 (90)	136 (95)	
Sought treatment elsewhere				
Yes (%)	522 (51)	410 (47)	84 (59)	0.009
No (%)	494 (49)	463 (53)	59 (41)	
Body Mass Index (kg/m^2)				
Underweight (%)	293 (32)	255 (33)	38 (29)	0.09
Normal (%)	483 (53)	417 (54)	66 (50)	
Overweight/Obese (%)	136 (15)	108 (14)	28 (21)	
Median BMI (Q3-Q1)	20(17.9 - 22.9)	20(17.9-22.8)	20.7(18.1-23.9)	0.05

3.3 Distribution of Patient, Health system and Total delay in Days

Overall patients across all age groups experienced higher patient delay compared to System delay as such patient delay contributed a larger proportion to the total delay. The distribution of all types of delay stratified by HIV status across different age groups is shown in **Figure 2**.

Figure 4: Median delay by HIV status across age groups



3.3.1 Patient delay

Longer patient delays were experienced among patients who were HIV positive compared to HIV negative patients (28 days (IQR, 21-56) vs. 21 days (IQR,14-42) days; p<0.0001). In particular, longer patient delays were experienced by HIV positive patients within the age groups of 18-29 and 30-44 years than their HIV negative counterparts. Significantly longer patients delays were further observed among HIV positive patients in the upper middle class compared to HIV negative patients of the same class (28 (IQR: 21-56) vs. 21 (IQR: 14-28) days; p<0.0001). HIV positive patients who neither smoked nor used alcohol had significantly longer delays than HIV negative patients with the same characteristics (28 (IQR: 21-56) vs. 21 (IQR: 14-42) days; p=0.0001) and (28 (IQR: 21-56) vs. 21 (IQR: 14-35) days; p=0.0002) respectively). Furthermore, HIV positive patients who were not taking cotrimoxazole or had sought treatment elsewhere had significant longer patient delays than HIV negative patients with similar characteristics. **Table 2** shows the distribution of patient delays in days stratified by HIV status.

Table 2: Distribution of Patient delay in days by HIV Status

Characteristic	HIV Positive		HIV Negative		P-Values
	n	*Median (Q3-Q1)*	*n*	*Median (Q3-Q1)*	
Overall	870	28(21-56)	143	21(14-42)	0.0001
Age (years)					
18-29	194	28 (21-56)	31	21 (14-28)	0.01
30-44	492	28 (21-56)	52	21 (14-28)	0.0005
>45	183	28 (21-56)	60	28 (14-56)	0.17
Sex					
Male	294	28 (21-56)	70	28 (14-49)	0.04
Female	601	28 (21-56)	73	21 (14-42)	0.0004
Socio-economic status					
Poor	294	28 (21-56)	51	21 (14-35)	0.1
Lower middle	271	28 (21-49)	45	28 (14-42)	0.5
Upper middle	292	28 (21-56)	44	21 (14-28)	<0.0001
Employment Status					
Unemployed	532	28 (21-56)	63	28 (14-56)	0.04
Employed	337	28 (14-35)	80	21 (14-28)	0.01
Ever smoked					
Yes	193	28 (21-56)	53	21 (14-42)	0.3
No	677	28 (21-56)	90	21 (14-42)	0.0001
Ever used alcohol					
Yes	237	28 (21-56)	53	28 (14-49)	0.08
No	631	28 (21-56)	90	21 (14-35)	0.0002
Body Mass Index (kg/m^2)					
Underweight	255	28 (21-56)	38	28 (21-56)	0.21
Normal	416	28 (21-56)	66	21 (14-42)	0.04
Overweight/obese	107	28 (14-56)	28	14 (14-28)	0.01
Currently on cotrimoxazole					
Yes	113	28 (21-56)	1	56 (56-56)	0.57
No	735	28 (21-56)	137	21 (14-42)	0.0006
Sought treatment elsewhere					
Yes	454	28 (21-56)	59	21 (14-28)	<0.0001
No	401	28 (14-42)	81	21 (14-42)	0.3
Hospital					
Baragwanath	398	28 (21-56)	78	21 (14-42)	0.01
Klerksdorp	285	35 (28 - 56)	21	28 (14-56)	0.04
Selby	187	28 (21 - 42)	44	21 (14-39)	0.5

3.3.2 Health system delay

The median system delay days for HIV positive was 2 days (IQR: 1-10) and that of HIV negative patients was 2 days (IQR: 1 - 6). There was no significant difference in median days of system delay for HIV positive compared to HIV negative patients (P=0.41). The same scenario of non-significance difference between the median health system delays for HIV positive patients compared to HIV negative patients was observed for all other patient's characteristics. **Table 3** shows the distribution of health system delay in days by HIV status.

Table 3: Distribution of Health system delay in days by HIV Status

Characteristic	HIV Positive		HIV Negative		P Value
	n	Median (Q3-Q1)	n	Median (Q3-Q1)	
Overall	480	2(1-10)	55	2 (1 - 6)	0.41
Age (years)					
18-29	110	2 (1-20)	15	1 (0-6)	0.3
30-44	267	2 (1-10)	15	2 (1-4)	0.3
>45	103	3 (0-9)	25	4 (1-7)	0.7
Sex					
Male	145	3 (1-9)	29	2 (1-6)	0.6
Female	335	2 (1-10)	26	1.5 (1-7)	0.4
Socio-economic status					
Poor	139	3 (1-10)	19	1 (0-6)	0.1
Lower middle	150	2 (1-10)	20	2 (1-4.5)	0.7
Upper middle	185	3 (1-11)	16	5 (1-8.5)	0.3
Employment Status					
Unemployed	306	2 (0-9)	27	1 (0-3)	0.1
Employed	174	3 (1-12)	28	4 (2-7)	0.7
Ever smoked					
Yes	96	2 (1-6)	19	2 (1-4)	0.8
No	384	3 (1-11.5)	36	3 (1-6.5)	0.5
Ever used alcohol					
Yes	131	3 (1-8)	22	2 (1-6)	0.96
No	348	2 (1-11.5)	33	2 (1-6)	0.3
Body Mass Index (kg/m^2)					
Underweight	159	2 (1-11)	20	2.5 (1-7)	0.8
Normal	213	3 (1-10)	24	2 (0-6)	0.3
Overweight/obese	56	4.5 (1-13)	8	2.5 (1-7)	0.5
Currently on cotrimoxazole					

Yes	67	6 (1-22)	1	1 (1-1)	0.4
No	397	2 (1-9)	51	2 (1-6)	0.7
Sought treatment elsewhere					
Yes	287	5 (1-20)	30	4.5 (1-10)	0.5
No	193	1 (0-4)	25	1 (0-3)	0.7
Hospital					
Baragwanath	215	3 (1-14)	30	2.5 (1-7)	0.6
Klerksdorp	203	1 (0-7)	16	1 (1-4.5)	0.8
Selby	62	4 (0- 9)	9	3 (0- 4)	0.2

3.3.3 Total delay

Overall, HIV positive patients had significantly longer total median delay relative to the HIV negative (39, IQR: 28-74 vs. 32, IQR: 21 – 56; p =0.02). Longer total median delays were significantly higher among poor HIV positive patients compared with the poor HIV negative (31.5, IQR: 22-82 vs. 27, IQR: 18-35; p< 0.03). Longer total median delays were also experienced by HIV positive patients who never smoked compared to HIV negative patients of the same category (41.5, IQR: 28-75 vs. 34.5, IQR: 21-51; p< 0.02). Furthermore, HIV positive patients who had sought treatment elsewhere had longer total median delays than the HIV negative patients of the same characteristics (56, IQR: 30-89 vs. 33.5, IQR: 27-57; p< 0.003). There was no significant difference in the median total delays in days with regard to age, gender, employment status, alcohol use, body mass index, type of hospital and use of cotrimoxazole between the HIV positive and HIV negative patients as shown in **Table 4**:

Table 4: Distribution of Total delay in days

Characteristic	**HIV Positive**		**HIV Negative**		**P Value**
	n	**Median (Q3-Q1**	**n**	**Median (Q3-Q1**	
Overall	478	39(28-74)	55	32(21-56)	0.02
Age (years)					
18-29	110	40.5 (28-87)	15	29 (16-55)	0.07
30-44	265	37 (28-69)	15	28 (21-45)	0.06
>45	103	43 (28-72)	25	35 (28-57)	0.36
Sex					
Male	145	34 (27-84)	29	32 (23-57)	0.24
Female	333	42 (28-72)	26	34.5 (21-45)	0.05

Socio-economic status					
Poor	138	31.5 (22-82)	19	27 (18-35)	0.03
Lower middle	149	32 (28-59)	20	43.5 (29-57)	0.69
Upper middle	185	44 (29-78)	16	33.5 (22-59.5)	0.1
Employment Status					
Unemployed	304	45.5 (29-84.5)	27	42 (28-57)	0.19
Employed	174	31 (23-57)	28	27.5 (19.5-40)	0.13
Ever smoked					
Yes	96	33 (22.5-69)	19	31 (23-57)	0.56
No	382	41.5 (28-75)	36	34.5 (21-51)	0.02
Ever used alcohol					
Yes	130	43 (27-85)	22	30 (27-57)	0.16
No	347	39 (28-70)	33	34 (21-47)	0.06
Body Mass Index (kg/m^2)					
Underweight	159	42 (28-70)	20	34.5 (28-56)	0.44
Normal	212	37.5 (28-78)	24	31.5 (22-60)	0.18
Overweight/obese	55	39 (21-77)	8	28.5 (18.5-38.5)	0.15
Currently on cotrimoxazole					
Yes	67	60 (31-99)	1	57 (57-57)	0.89
No	395	35 (28-62)	51	32 (23-55)	0.08
Sought treatment elsewhere					
Yes	285	56 (30-89)	30	33.5 (27-57)	0.003
No	193	29 (21-52)	25	32 (17-43)	0.88
Hospital					
Baragwanath	215	32 (24-73)	30	28.5 (21-55)	0.05
Klerksdorp	201	56 (29-85)	16	37.5 (21-57)	0.07
Selby	62	29 (24-48)	9	35 (32-45)	0.08

3.4 Predictors of Prolonged Patient delay

Univariable and multivariable analyses were done to determine the predictors of prolonged patient delay in the diagnosis and treatment of suspected TB cases.

3.4.1 Univariable analysis

To understand the relationship between each predictor variable and the outcome, prolonged patients delay, the odds ratios of each predictor variable stratified by HIV status were calculated. For patients who were HIV positive, significant results were obtained for socio-economic status, crowding index, employment status, body mass

index, type of hospital, taking cotrimoxazole and sought treatment elsewhere. However, for HIV negative patients, only employment status predicted the prolonged patient delay outcome.

HIV positive patients in the upper middle class had higher odds of experiencing prolonged patients delay (OR 1.6, 95% C.I: 1.1-2.2) compared to the HIV positive patients who belonged to the poor class of socio-economic status. Crowding index was protective since a unit increase in crowding index was found to be associated with reduced odds of prolonged patient delay protective among HIV positive patients (OR 0.8, 95% C.I: 0.7- 0.9). The odds of prolonged patient delay were high among the unemployed patients in both HIV positive (OR 2.2, 95%CI: 1.7- 3.01) and HIV negative (OR 2.6, 95%CI: 1.2-5.5) groups.

HIV positive patients were also more likely to experience prolonged patient delay if they were taking cotrimoxazole (OR1.8, 95% CI: 1.2- 2.7), had sought prior treatment elsewhere (OR 2.2, 95% CI: 1.7- 2.9), were admitted to Tshepong (OR 2.3, 95% CI: 1.7- 3.1) and were underweight (OR 1.7, 95% CI: 1.2 - 2.3).

3.4.2 Multivariable analysis

In multivariate analysis, crowding index, employment status, body mass index, taking cotrimoxazole and sought treatment elsewhere significantly predicted the prolonged patient delay for HIV positive patients while employment status predicted the outcome for HIV negative patients. Among the HIV positive patients, there were no changes in the Odd of delay for crowding index in both the Univariate and multivariate model. However, minor decreases in the odds ratio were observed for body mass index, taking cotrimoxazole sought treatment elsewhere. The Adjusted Odds Ratio (AOR) of patient delay among the unemployed were slightly higher (AOR 2.6, 95% CI: 1.8- 3.8) in the multivariate model of HIV positive patients while the odds of delay remained the same in the multivariate model of HIV negative patients. **Table 5** shows the univariate and multivariate analyses for prolonged patient delay stratified by HIV status.

Table 5: Predictors of Prolonged Patient Delays (> 28 Days) in Tuberculosis Diagnosis and Treatment

Characteristics	HIV Positive				HIV Negative			
	Univariable	**P-Value**	**Multivariable**	**P-Value**	**Univariable**	**P-Value**	**Multivariable**	**P-Value**
	OR (95% CI)		*AOR (95% CI)*		*OR (95% CI)*		*AOR (95% CI)*	
Age_Cat (years)								
18-29	1.0		_	_	1.0			
30 - 44	0.9 (0.6-1.2)	0.4	_	_	0.9 (0.3- 2.7)	0.9	_	_
>45	1.1 (0.7-1.6)	0.7	_	_	2.1 (0.8- 5.7)	0.1	_	_
Gender								
Male	0.99 (0.7- 1.6)	0.9	_	_	1.3 (0.6- 2.7)	0.5	_	_
Female	1.0		_	_	1.0		_	_
Crowding Index	0.8 (0.7- 0.9)	0.002	0.8 (0.7- 0.9)	0.01	0.9 (0.7- 1.3)	0.6	_	_
Employment status								
Employed	1.0		1.0		1.0		1.0	
Unemployed	2.2 (1.7- 3.0)	<0.0001	2.6 (1.8- 3.8)	<0.0001	2.6 (1.2-5.5)	0.001	2.6 (1.2- 5.8)	0.02
Ever smoked								
Yes	0.9 (0.6- 1.2)	0.4	_	_	1.1 (0.5- 2.4)	0.8	_	_
No	1.0		_	_	1.0		_	_
Alcohol use								
Yes	1.1 (0.8- 1.5)	0.4	_	_	1.5 (0.7- 3.1)	0.3	_	_
No	1.0		_	_			_	_
BMI (kg/m^2)								
Normal	1.0		1.0		1.0		1.0	
Underweight	1.7 (1.2 - 2.3)	0.001	1.6 (1.1- 2.3)	0.01	1.9 (0.8 - 4.5)	0.12	1.7 (0.7- 4.1)	0.2

Overweight/Obese	1.02 (0.7- 1.6)	0.9	0.8 (0.5 - 1.3)	0.3	0.4 (0.1-1.5)	0.18	0.4 (0.1- 1.2)	0.1
Hospital								
Baragwanath	1.0		1.0		1.0		_	_
Klerksdorp	2.3 (1.7- 3.1)	<0.0001	1.4 (0.9- 2.1)	0.09	1.7 (0.6- 4.6)	0.3	_	_
Selby	0.9 (0.6- 1.3)	0.6	1.1 (0.7- 1.8)	0.6	1.02 (0.4- 2.3)	0.97	_	_
Sought treatment elsewhere								
Yes	2.2 (1.7- 2.9)	<0.0001	1.8 (1.2- 2.5)	0.002	0.7 (0.3- 1.4)	0.3	_	_
No	1.0		1.0		1.0		_	_
Cotrimoxazole								
Yes	1.8 (1.2- 2.7)	0.003	1.7 (1.04- 2.6)	0.03	_	_	_	_
No	1.0		1.0		_	_	_	_

3.5 Predictors of Prolonged Health system delay

Univariable and multivariable analyses stratified by HIV status were done to determine the predictors of prolonged health system delay in the diagnosis and treatment of suspected TB cases.

3.5.1 Univariable analysis

In the univariable analysis, we found that crowding index and sought treatment elsewhere were significant predictors of prolonged health system delay for the HIV positive patients while there was no significant predictor among the HIV negative patients.

Crowding index (OR 0.7, 95% CI: 0.6- 0.9) was found to be protective whereas HIV positive patients who had sought treatment elsewhere (OR 4.7, 95% CI: 2.9- 7.6) had higher odds of experiencing prolonged health system delay than those who never sought treatment.

3.5.2 Multivariable analysis

Crowding index and sought treatment elsewhere predicted prolonged health system delay among HIV positive patients in the multivariate analysis. Crowding index was protective (AOR 0.8, 95% CI: 0.7- 0.97) while patients who sought prior treatment had higher odds of prolonged health system delay relative to those who never sought treatment (AOR 4.5, 95% CI: 2.7- 7.3). **Table 6** shows the univariate and multivariate analyses for prolonged health system delay stratified by HIV status.

Table 6: Predictors of Prolonged System Delay (> 7 Days) in Tuberculosis Diagnosis and Treatment

Characteristics	HIV Positive				HIV Negative			
	Univariable	**P-Value**	**Multivariable**	**P-Value**	**Univariable**	**P-Value**	**Multivariable**	**P-Value**
	OR (95% CI)		*AOR (95% CI)*		*OR (95% CI)*		*AOR (95% CI)*	
Age_Cat (years)								
18-29	1.0		_	_	1.0		_	_
30 - 44	0.9(0.5- 1.4)	0.6	_	_	1.0	_	_	_
>45	0.9(0.5- 1.7)	0.8	_	_	1.3(0.3- 6.02)	0.8	_	_
Gender			_	_			_	_
Male	0.99(0.6- 1.5)	0.97	_	_	1.2(0.3- 4.8)	0.9	_	_
Female	1.0		_	_	1.0		_	_
Crowding Index	0.7 (0.6- 0.9)	0.002	0.8(0.7- 0.97)	0.03	1.3(0.7- 2.3)	0.5	_	_
Employment status							_	_
Employed	1.0		_		1.0		_	_
Unemployed	0.9 (0.6- 1.3)	0.5			0.5(0.1- 2.1)	0.3	_	_
Ever smoked			_				_	_
Yes	0.7 (0.4- 1.1)	0.1			1.2(0.3- 5.3)	0.8	_	_
No	1.0		_		1.0		_	_
Alcohol use			_				_	_
Yes	0.8 (0.5- 1.2)	0.3			1.7(0.4- 7.1)	0.5	_	_
No	1.0		_		1.0		_	_
BMI (kg/m^2)							_	_
Normal	1.0		_		1.0		_	_
Underweight	1.01 (0.6- 1.6)	0.95			1.7 (0.4 - 7.3)	0.5	_	_
Overweight/Obese	1.4 (0.7- 2.6)	0.3			1.0	_	_	_
Hospital			_				_	_

Baragwanath	1.0		_		1.0		_	_
Klerksdorp	0.7 (0.42- 0.99)	0.05	_		0.5(0.1- 2.6)	0.4	_	_
Selby	1.02(0.56- 1.8)	0.96	_		1	_	_	_
Sought treatment elsewhere							_	_
Yes	4.7(2.9- 7.6)	<0.0001	4.5(2.7- 7.3)	<0.0001	-	_	_	_
No	1.0		1		-		_	_
Cotrimoxazole							_	_
Yes	1.7(0.99- 2.9)	0.05			-	_	_	_
No	1.0		_		-	_	_	_

3.6 Predictors of Prolonged Total delay

Univariable and multivariable analyses were done to determine the predictors of prolonged total delay in the diagnosis and treatment of suspected TB cases.

3.6.1 Univariable analysis

During the univariable analysis for patients who were HIV positive, significant results were obtained for crowding index, employment status, type of hospital, taking cotrimoxazole and sought treatment elsewhere. However, for HIV negative patients, only employment status predicted the prolonged total delay outcome.

Higher odds of prolonged delay were experienced among the unemployed HIV positive patients (OR 1.95, 95% CI: 1.3-2.9) compared to the employed patients. The situation was the same among the unemployed HIV negative patients. However, the odds were much higher (OR 4.2, 95% CI: 0.9-19.5) for the group.

The odds of prolonged delay were lower with a unit increase in crowding index (OR 0.8, 95% CI: 0.7 -0.9) among the HIV positive group. HIV positive patients were also more likely to experience prolonged total delay if they were taking cotrimoxazole (OR 2.4, 95% CI: 1.4 -4.1), had sought prior treatment elsewhere (OR 4.5, 95% CI: 3.1-6.8) and were admitted to Tshepong (OR 1.9, 95% CI: 1.3-2.9).

3.6.2 Multivariable analysis

In multivariable analysis, employment status, taking cotrimoxazole and sought treatment elsewhere significantly predicted the prolonged total delay for HIV positive patients while there was no significant predictor for HIV negative patients. The odds of delay were higher for those who were taking cotrimoxazole (AOR 2.6, 95% CI: 1.4-4.8) and the unemployed (AOR 2.4, 95% CI: 1.5-3.8) HIV positive patients. Higher odds of delay were experienced among the HIV positive patients who sought treatment elsewhere (AOR 4.3, 95% CI: 2.7-6.6), although the odds were slightly lower in multivariate compared to univariate models. **Table 7** below shows the univariate and multivariate analyses for prolonged total delay stratified by HIV status.

Table 7: Predictors of Prolonged Total Delay (> 35 Days) in Tuberculosis Diagnosis and Treatment

Characteristics	HIV Positive				HIV Negative			
	Univariable	**P-Value**	**Multivariable**	**P-Value**	**Univariable**	**P-Value**	**Multivariable**	**P-Value**
	OR (95% CI)		*AOR (95% CI)*		*OR (95% CI)*		*AOR (95% CI)*	
Age_Cat (years)								
18-29	1.0		_		1.0		_	
30 - 44	1.0(0.6-1.6)	0.995	_		1.0 (0.2 - 4.6)	1.0	_	
>45	1.4(0.8-2.3)	0.28	_		1.9 (0.5-6.9)	0.4	_	
Gender								
Male	0.8(0.6-1.3)	0.4	_		0.8 (0.3 -2.5)	0.7	_	
Female	1.0		_		1.0		_	
Crowding Index	0.8 (0.7 -0.9)	0.02	0.9 (0.7 -1.03)	0.1	1.1 (0.6 -1.8)	0.8	_	
Employment status								
Employed	1.0		1.0		1.0		1.0	
Unemployed	1.95 (1.3-2.9)	0.001	2.4 (1.5-3.8)	0.001	3.8 (1.2 -11.8)	0.02	4.2 (0.9-19.5)	0.07
Ever smoked								
Yes	0.8 (0.5-1.2)	0.3	_		0.8 (0.3 -2.6)	0.7	_	
No	1.0		_		1.0		_	
Alcohol use								
Yes	1.1(0.7-1.6)	0.7	_		1.1 (0.4 -3.2)	0.9	_	
No	1.0		_		1.0		_	
BMI (kg/m^2)								
Normal	1.0				1.0		_	
Underweight	1.1 (0.7 -1.7)	0.6	_		1.15 (0.35 -3.8)	0.8	_	
Overweight/Obese	1.2(0.6 -2.1)	0.6	_		0.5 (0.1 - 2.5)	0.4	_	
Hospital								
Baragwanath	1.0		1.0		1.0		1.0	

Klerksdorp	1.9 (1.3-2.9)	0.001	1.1 (0.7-1.9)	0.6	2 (0.6-6.9)	0.3	0.7 (0.1-3.7)	0.6
Selby	0.6 (0.3-1.02)	0.1	0.8 (0.4 -1.5)	0.5	1.6 (0.4-7.3)	0.5	2.4 (0.3-17.5)	0.4
Sought treatment elsewhere								
Yes	4.5 (3.1-6.8)	<0.0001	4.3 (2.7-6.6)	<0.0001	1.4 (0.5 -4.04)	0.6	_	
No	1.0		1.0		1.0		_	
Cotrimoxazole								
Yes	2.4 (1.4 -4.1)	0.003	2.6 (1.4-4.8)	0.003	-		_	
No	1.0		1.0		-		_	

CHAPTER FOUR: DISCUSSION

4.1 Distribution of delay

There is limited research from South Africa that examines delays in TB diagnosis and treatment by HIV status despite the high HIV and TB burden. Our study found a higher patient and total delays in HIV positive patients compared to the HIV negative. To the contrary, a cross-sectional study conducted in Thailand found shorter patient and total delays in HIV positive patients compared to the HIV negative (36). According to the Thailand study, these shorter delays in HIV positive patients were attributed to high health insurance coverage, easy access and acquaintance with the services provided by the healthcare facilities (36). In our set-up, it may be that the longer delays among the HIV positive would have resulted from several factors including a poor understanding of TB symptoms, seeking care elsewhere before TB diagnosis and affordability as suggested by the high unemployment rates. Additionally, health care workers in Thailand may have had a higher index of TB suspicion for HIV positive patients resulting in earlier diagnosis and treatment of TB cases which led to shorter delays (48). However, our distribution of delays concurs with the results of a study undertaken in Hohoe municipality in Ghana (23) and a descriptive cross-sectional study conducted in Zimbabwe (17). The similarity of the distribution of our delays to the results found in these studies could be attributed to the premise that both settings share similar demographic characteristics and experience a high burden of TB and HIV similar to our study setting.

Studies have demonstrated that there is no association between prolonged patient delay and HIV status (17, 23) while other authors have documented that HIV positive patients are more likely to have reduced odds of prolonged patient delay than the HIV negative counterparts (36). However, our comparison of the delays among HIV positive and HIV negative patients revealed that higher odds of prolonged delays were experienced among patients who were HIV positive. Furthermore, the findings revealed that HIV status acts as an effect modifier when prolonged patient delay is investigated against other exposures like whether the patient sought treatment prior to TB diagnosis. Similar results were found from a study conducted in an HIV epidemic area, whose aim was to investigate the association

between HIV awareness and patient-related delay in diagnosis and treatment of TB (46). According to the study, confusion between the signs and symptoms of TB and HIV among HIV positive patients results in delays in seeking treatment for TB (46). Longer patient delays among HIV positive patients could have also been a result of stigma and discrimination. Studies have revealed that enacted and internalised stigma was correlated with delays in seeking care after testing HIV-positive (14, 37).

The level to which health workers suspect TB in a patient, also known as the Index of TB suspicion by health care workers, is among the main factors that affect health system delay (16). In developing countries where TB prevalence is very low, there is a low index of TB suspicion by health care workers which results in longer health system delays (47). On the contrary, the index of TB suspicion among health care workers in TB endemic settings is high and this result in shorter health system delays (48). Our results showed no significant differences in the median health system delay by HIV status. This could imply that in our setting, the health system manages TB cases in the same way regardless of HIV status. Our results concur with results found in studies conducted in Ghana and India (23, 26). However, a study carried out in Northwest Ethiopia in the year 2014 found different results from our study in which HIV negative patients had longer health system delay than HIV positive patients (8). Possible explanations in such settings could be that the HIV positive TB patients might have presented with severe symptoms indicative of TB due to co-infection with HIV and also there might have been high levels of awareness among health workers regarding HIV and TB co-infection which made it easier to suspect TB among HIV cases (8). The data for this study was collected between 2006 to 2009.During such period, healthcare worker's awareness regarding HIV and TB co-infection was not as high as during the time the Northwest Ethiopian study was conducted (8) when there was rapid awareness regarding co-infections of HIV and TB. This could be the key reason why differences in the results are observed from our study and recent studies.

4.2 Determinants of Delay

The odds of prolonged patient delay were twice as much among the unemployed patients compared to the employed in both HIV positive and HIV negative patients. Similarly, higher

odds of prolonged total delay were experienced among the unemployed patients. A systematic review conducted by Cai and colleagues revealed similar results with our findings (49). Furthermore, a cohort study conducted by Dos Santos in Brazil's semi-urban area almost the same setting as our study area found same results with our study (39). According to Dos Santos, the majority of employed patients had attained some education and had access to TB awareness programs (39). This made it easy for them to quickly notice the signs and symptoms of TB and understand the benefits of early diagnosis and treatment. In our study setting, however, employment is highly linked to SES. Therefore, unemployment which may ultimately lead to low income may reduce the likelihood of potential TB patients to seek care after experiencing signs and symptoms of TB compared to the employed who may have adequate financial resources to seek medical attention (50).

HIV positive patients who were underweight had higher odds of prolonged patient delay. However, we did not experience any significant difference in the odds of prolonged total delay and prolonged system delay with regard to BMI. To the contrary, different results emanated from a study conducted in Brazil where patients with weight loss which indicates underweight BMI reduced odds of prolonged patient and total delay (39). Such difference could occur because BMI has been associated with SES in many resources limited settings where normal or overweight individuals are considered of high SES unlike the underweight (17). Being underweight could, therefore, have a similar effect as being of low SES where resources to seek medical care after experiencing signs of TB could be a challenge (18, 19).

Our study revealed that HIV positive patients were more likely to experience prolonged patient, health system and total delays if they had sought prior treatment elsewhere. Studies conducted in Ghana, Angola and Thailand reported the same and the reason being that patients who visit different multiple health care providers make it difficult for the providers to reach a prompt TB diagnosis (18, 19, 23). Similar explanations could apply in our study setting. In addition to such explanation, patients in our study would have been assured of getting better upon seeking treatment from other sources. The period they anticipate to get better upon receiving prior treatment would therefore lead to delays. However, other authors have attributed delays associated with seeking prior treatment to nonspecific test results and atypical clinical features (51, 52).

We found that higher odds of prolonged patient and total delay were experienced by HIV positive patients who were taking cotrimoxazole. HIV infection leads to opportunist infections most of which are bacterial in nature(1). In an attempt to lessen the suffering from the bacterial opportunist infections most of the patients seek antibiotics of which the common one is cotrimoxazole. Taking cotrimoxazole which potentially has some anti-TB infection remedy could have resulted in lessening the symptoms for a short period, and the patients could have thought that they would recover which ultimately led to the prolonged delay. Authors have reported similar findings in both developed and developing countries (8, 21, 24, 25).

Crowding index was protective of both prolonged patient and health system delay among HIV positive patients. A study conducted in the Bale zone of south-east Ethiopia found similar results (15). Since overcrowding is associated with ease of TB transmission (48, 53), it may imply that healthcare workers treated suspected TB patients who came from overcrowded houses with urgency to prevent further transmission and this resulted in lower odds of prolonged health system delay. Likewise, the fear of spreading TB to other household members and support from other family members could have been the reason why crowding index was found to be protective of prolonged patient delay.

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion and recommendations

This study has compared the determinants of delay in the diagnosis and treatment of suspected TB among HIV positive and HIV negative patients in a setting where there is a high burden of TB and HIV. This is a critical comparison since it relates to individual patient outcomes and TB transmission in resource-limited and dynamic societies. Higher patient delays compared to health system delays suggests that health promotion interventions targeting patient delays could be more effective at improving individual patient outcomes and control the spread and the negative impacts associated with TB infection. There is, therefore, a need for more community awareness interventions aimed at sensitising the communities about the signs and symptoms suggestive of TB disease and the importance of seeking medical care in a timely manner. Targeted public health interventions focusing on HIV positive people should also be employed since there is a high risk of TB and HIV co-infection.

Since HIV positive patients had higher odds of experiencing prolonged health system delay than the HIV negative patients, deliberate efforts should be made to strengthen TB diagnostics services among HIV positive patients. Regular refresher training courses that address the importance of high index of suspicion for TB, particularly among HIV positive patients, should be provided to healthcare workers. Referral systems should be strengthened such that health facilities that do not offer TB diagnostic services should be able to promptly refer the suspected patients to a hospital that provide the service on time. Alternatively, the government may empower and actively involve the private General Practitioners (GPs) in the diagnosis of TB since the majority of patients visit a GP during their illness.

5.2 Strengths and limitations of the study

The strengths and limitations of the study are discussed based on the classification of exposures and outcomes; applicability of the results to other settings; confounding and effect modification and appropriateness of analysis methods.

A significant strength in our observed variables is that the data are consistently updated, corrected, and checked for inconsistencies. However, there are some biases related to the classification of exposures and outcomes. Firstly, information on occurrence and duration of symptoms suggestive of TB was prone to recall bias because it was self-reported. This could have affected the calculation of patient delay since the participants may not correctly remember the first day the first symptoms of TB occurred. Secondly, the use of differential diagnosis of TB as an inclusion criterion could have resulted in misclassification on study participants hence leading to selection bias. Furthermore, use of secondary data meant that we had no control of data quality during the data collection phase and other information on potential confounders was not collected.

The data was collected from patients who were hospitalised in the three hospitals. Other potential patients who could have formed part of our study may have opted for other hospitals, and some may not even seek any medical care and this subjected our study to selection bias. Additionally, data may be outdated since it was collected from 2006 to 2009.In recent years many developments in diagnosis and treatment of TB have been initiated and the results may therefore not applicable in such circumstances. Furthermore, since data was collected in a high TB and HIV incidence area, the findings may not be generalisable to other settings with a low burden of TB and HIV.

Although we had a relatively smaller number of HIV negative patients compared to the HIV positive, we used logistic regression models which mitigated this discrepancy as it compares proportions as opposed to actual numbers. Furthermore, effect modification was investigated and dealt with through stratified analysis. Additionally, multiple logistic regression was conducted to control for confounding variables.

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APPENDICES

Appendix 1: Senate Plagiarism Policy

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

I **Victor Kanje** (Student number: **1228323**) am a student registered for the degree of **Master of Science in Epidemiology and Biostatistics** in the academic year **2015/2016**.

I hereby declare the following:

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

Signature:  Date: **31/03/2017**

Appendix 2: Ethics Clearance Certificate

R14/49 Mr Victor Kanje et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160548

NAME: (Principal Investigator)	Mr Victor Kanje et al
DEPARTMENT:	Public Health
PROJECT TITLE:	Determinants of Delay in Diagnosis and Treatment of Suspected Tuberculosis in HIV Negative and HIV Positive Patients in South Africa
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Eustasius Musenge

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/05/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year.

Principal Investigator Signature

Date 03/06/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES