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Risk factors for prevalent tuberculosis in HIV-infected patients attending a fee-for-service HIV clinic in inner city Johannesburg, South Africa

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RISK FACTORS FOR PREVALENT TUBERCULOSIS IN HIV-INFECTED PATIENTS ATTENDING A FEE-FOR-SERVICE HIV CLINIC IN INNER CITY JOHANNESBURG, SOUTH AFRICA

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A research report submitted in partial fulfillment of the requirements for the degree of
Master of Science in Epidemiology and Biostatistics

University of the Witwatersrand,
Faculty of Health Sciences, School of Public Health
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DECLARATION

I, Lucy Connell, declare that this Research Report is my own work. It is being submitted for the degree of Master of Science in Epidemiology and Biostatistics at the University of the Witwatersrand, Johannesburg. No prior submissions of this material have been made for any degree or examination at this or any other university.



Lucy Connell

9 May 2014

ABSTRACT

Introduction

HIV-associated TB is curable with standard TB therapy and yet it is the leading cause of illness and death in patients infected with HIV. Coinfection with HIV poses considerable challenges to early diagnosis of TB in HIV-infected people and diagnostic delay and the rapidly progressive TB associated with HIV results in rapid clinical deterioration and increased mortality. There is an urgent need for research to identify risk factors for TB in HIV-infected people in order to refine diagnostic algorithms for the early and accurate diagnosis of tuberculosis in HIV-positive patients.

The aim of this study was to determine the prevalence of TB, and identify factors associated with prevalent TB in HIV-infected adults paying a subsidized, all-inclusive monthly fee for HIV care in a private setting in downtown Johannesburg – a unique sub-population.

Material and Methods

This study was a retrospective, cross-sectional, secondary analysis of data extracted from the routine electronic medical records of HIV-infected adults who attended ZuziMpilo from August 2009 to December 2011. The outcome of interest was prevalent TB at the time of enrollment into care and exposures included age, sex, ethnicity, CD4 count, WHO Clinical Stage, BMI, alcohol and tobacco use history, level of education, employment status, monthly income, monthly cell phone expenditure, medical insurance status, source of funding for HIV care and source of knowledge about ZuziMpilo Medical Centre.

Multivariable logistic regression modeling was used to determine risk factors for prevalent TB at the time of enrollment.

Results

Approximately 8 out of every 100 HIV-infected adults enrolling at ZuziMpilo from August 2009 to December 2011 had prevalent TB disease (8.24%). Significant predictors for prevalent TB included BMI categorised as non-obese, CD4 count <350 cells/mm^3 and duration on HAART of less than six months. With respect to BMI, individuals who were not obese had greater risk of prevalent TB, the risk increasing in a dose response fashion as the BMI decreased. Compared to obese patients, overweight patients were 2.8 times as likely (aOR = 2.83, CI 1.06 – 7.52, p = 0.037), normal weight patients were more than 3.7 times more likely (aOR = 3.72, CI 1.44 – 9.60, p = 0.007) and underweight patients were more than 6.4 times more likely to have prevalent TB (aOR = 6.42, CI 2.33 – 17.70, p = 0.000). A CD4 count of < 200 cells/mm^3 predicted an 11.3 times increased risk of prevalent TB relative to CD4 count greater than 350 cells/mm^3 (aOR = 11.27, CI 4.84 – 26.28, p = 0.000). Patients treated with HAART for longer than 6 months were significantly less likely to have prevalent TB than HAART-naïve patients (aOR = 0.47, CI 0.23 – 0.98, p = 0.043).

Conclusion and Recommendations

This study corroborates the growing body of evidence that underpins several key recommendations that have the potential to reduce mortality from TB in those people infected with HIV; vigilant and regular routine TB screening in HIV-infected patients at all CD4 counts and especially in those with profound immunosuppression and in the first three

to four months following HAART initiation, the urgent development and distribution of more sensitive and point of care diagnostic tests for TB in HIV-infected patients at all levels of health care (most especially primary health care facilities) and the importance of initiation of HAART before CD4 counts drop below 350 cells/mm^3. This study highlights that BMI is a useful proxy marker of TB risk among HIV-positive individuals. Height and weight are easily assessed anthropomorphic measures and should be conducted routinely in all patients at regular intervals.

This study has described a unique population with the capacity to pay a subsidised monthly fee for their HIV care and thus the results may not be generalisable to the large population of HIV-infected adults in South Africa, who receive free-of-charge health care in public sector facilities. However, they may certainly be generalisable to other clinics that provide services for a fee and this information may be especially important if this model is replicated and scaled up in private and semi-private facilities around the country.

DEDICATION

This work is dedicated to my beloved husband, Paul Boulle.

ACKNOWLEDGEMENTS

I thank my two supervisors, Dr Eustasius Musenge and Dr Neil Martinson for their input, guidance and patience in the preparation of this report.

I would also like to thank the staff of the ZuziMpilo Medical Centre for permission to use the clinic's data and for the generous contribution of their time and knowledge to help me navigate my way through the data base and to locate source documents. In particular, I would like to recognise the assistance of Dr Limakatso Lebina, Project Director of ZuziMpilo Medical Centre. I am grateful to Ms Francisca Havenith, the Product Specialist at Advanced Biological Laboratories (ABL) S.A., who helped me understand the architecture of the TherapyEdge^{TM} database so that I could extract the data set used in this study. Finally, I am most grateful to all the patients of ZuziMpilo Medical Centre whose data I have used.

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GLOSSARY

AFB	Acid-fast bacillus. This term is a synonym for bacteria of the Genus *Mycobacteria*, which includes the causative organism of tuberculosis, *M. tuberculosis*, and refers to the physical property of retaining colourant dyes despite washing with acid.
AIDS	Acquired Immunodeficiency Syndrome
BMI	Body mass index
CD4	CD4 cell or T4 helper lymphocyte
CI	Confidence interval
CSV	Comma separated value
ETR.Net	Electronic Tuberculosis Register
HAART	Highly active antiretroviral treatment
HIV	Human immunodeficiency virus
NHLS	National Health Laboratory Service
NICD	National Institute for Communicable Diseases
IRR	Incidence rate ratio
IQR	Interquartile range
OR	Odds ratio
PEPFAR	Presidents Emergency Plan for AIDS Relief
Prevalent TB	The term refers to the number of **existing** TB cases identified at a specific point in time, in contrast to the number of **new** TB cases identified within a specific time period (incident TB). In this study the term has a specific definition related to the time frame and evidence for the diagnosis.

SD	Standard deviation
SNTB	Culture-confirmed tuberculosis that was initially sputum smear-negative
TB	Tuberculosis
WHO	World Health Organisation
WHO Clinical Stage	World Health Organisation-devised classification of HIV disease into four progressive clinical stages reflecting deteriorating immune system function. (1)
ZuziMpilo	ZuziMpilo Medical Centre

1. INTRODUCTION

This chapter illustrates the burden of TB and HIV coinfection and provides a justification for this study, presenting a literature review that explores the reported TB prevalence among HIV-infected individuals attending dedicated HIV clinics and discussing evidence for factors reported to predict TB in the general population and among HIV-infected populations specifically.

1.1. Background

1.1.1. ***The burden of TB globally and in sub-Saharan Africa***

Tuberculosis (TB) remains the leading infectious cause of death worldwide, despite major progress in reducing the number of TB cases and deaths in the past two decades (2). This is particularly true in Africa, a region responsible for a quarter (25%) of the 8.7 million new cases of TB reported in 2011 (2). This follows an unprecedented surge in the incidence of TB in sub-Saharan Africa in particular, fuelled largely by the HIV epidemic, where annual TB incidence has doubled and the number of TB cases and TB-related deaths has tripled since 1990 (3).

1.1.2. ***HIV and TB coinfection***

HIV infection is the most potent risk factor for tuberculosis and drives the TB epidemic at population level (4-7). A recent World Health Organization (WHO) analysis of the

proportion of TB cases coinfected with HIV confirms that HIV-infected individuals are 20 times more likely than HIV-seronegative people to develop active TB in countries with high HIV prevalence (8). The increased risk of TB disease in HIV-infected individuals manifests soon after infection, doubling within the first year after HIV infection, even before CD4 counts decline (9). The rising prevalence of HIV has dramatically increased the incidence of TB, both in people living with HIV as well as possibly indirectly in those who are HIV-negative because of the increased pool of infectious individuals in the population (10)..

1.1.3. ***HIV and TB in South Africa***

South Africa has the highest number of people infected with HIV in the world (11), with an estimated 5.6 million HIV-infected individuals in 2011(12). According to the WHO Global Tuberculosis Report 2012, the country also has the highest TB incidence rate; 993 per 100 000 in 2011 (2). Many patients with TB are coinfected with HIV. In 2011, 65% of the TB patients for whom HIV status was known were coinfected with HIV (2).

The incidence of TB appears to be dropping since it reached a peak in 2009. The District Health Barometer reports a trend of decreasing numbers of new cases of pulmonary smear-positive TB since 2009 (13). Similarly, recent analysis by the National Institute for Communicable Diseases (NICD), of all the microbiological testing undertaken for suspected TB cases between 2004 and 2012, conducted exclusively by the National Health Laboratory Service (NHLS), showed that national TB incidence (including pulmonary and extra-pulmonary TB) peaked in 2009 and subsequently decreased to 2006 rates by 2012.

The reduction in TB rates since 2009 correlates with the scale up in the ART programme, despite the lack of decline in HIV prevalence rates over the same period (14).

1.1.4. ***HIV-associated TB Mortality***

The syndemic interaction between HIV and TB has deadly consequences around the world (15). TB is the leading cause of morbidity and mortality in HIV-infected adults in sub-Saharan Africa (7, 16). HIV-infected people have more rapidly progressive TB and a higher TB-associated mortality than their HIV-negative counterparts (17, 18). Thus, in 2011, HIV-associated TB accounted for 31% of deaths among incident TB cases globally, even though only 13% of all incident cases were coinfected (2).

HIV-infection alters the clinical and radiological presentation of TB, making diagnosis more difficult (19, 20). Consequently, active TB is often not diagnosed in HIV-infected patients, a reality borne out by evidence arising from postmortem studies of HIV/AIDS patients in several sub-Saharan African countries, including South Africa. These studies reveal extremely high proportions of deaths with undiagnosed and often disseminated TB (21-23). It is likely that official figures underestimate the contribution of TB to mortality in HIV-infected patients.

1.1.5. ***Diagnosis of TB***

Sputum smear microscopy, the traditional method of diagnosing TB rapidly, is less sensitive in HIV-infected patients because they have frequently pauci-bacillary disease, i.e.,

fewer acid fast bacilli (AFB) detectable in their sputum (24, 25). HIV-infected adults with TB are twice as likely to have sputum smear-negative but culture positive TB, compared with HIV negative adults (26). Atypical clinical presentations and radiological features, together with reduced sensitivity of sputum smear microscopy and long waiting time (2 to 6 weeks) for mycobacterial culture results contribute to delayed diagnosis of TB in HIV-infected patients (27). Moreover, smear-negative TB (SNTB) has worse prognosis (28) in part due to delays in diagnosis and treatment initiation (27). However, rapid, accurate, novel molecular methods to diagnose TB have recently become available. South Africa is the leading adopter of the WHO-endorsed *Xpert MTB/RIF*, a rapid molecular test that can diagnose TB and rifampicin resistance within 100 minutes (2). Despite the national roll out of *Xpert MTB/RIF* in South Africa since March 2011, sputum smear microscopy remains the mainstay of diagnosis in many facilities countrywide (29).

Data from the South African electronic TB register (ETR.Net) bear witness to the high proportion of missed TB diagnoses in HIV positive patients (30). In 2007, burgeoning access to direct measurements of the prevalence of HIV in TB patients worldwide prompted the revision of the risk of developing TB in HIV-positive patients as compared with HIV-negative patients in countries with high prevalence, generalized HIV epidemics. The incidence rate ratio (IRR) was revised upwards from 6 to 20.6 (8). However, in the 2010/2011 financial year, only 67.7%, of newly diagnosed HIV-infected patients (approximately 940 000 of 1.4 million) were screened for TB. Over the same period the District Health Information System recorded 100 000 new HIV-positive patients with confirmed TB (7.1%). Although the higher rates of smear negative TB in HIV-positive

individuals, under reporting and poor data quality contribute to this low rate of HIV-positive patients with confirmed TB, the large gap between the number of expected and reported cases is yet another confirmation of the extent to which TB is under diagnosed in HIV-positive patients (13).

1.1.6. **ZuziMpilo Medical Centre**

The ZuziMpilo Medical Centre (ZuziMpilo) is a private clinic in downtown Johannesburg that offers fee-for-service health care for people living with HIV. ZuziMpilo offers voluntary counselling and testing for HIV, a wellness programme that caters for HIV-infected people who are not yet eligible for antiretroviral treatment and antiretroviral treatment. The setting of ZuziMpilo, and the TB-related services it offers, is described in more detail in Chapter 2, Material and Methods.

1.2. Statement of problem

HIV-associated TB is curable with standard TB therapy (15) and yet it is the leading cause of illness and death in the 5.6 million South Africans estimated to be infected with HIV. Coinfection with HIV poses considerable challenges to early diagnosis of TB in HIV-infected people. In the face of diagnostic delay, rapidly progressive TB associated with HIV can result in rapid clinical deterioration and increased mortality, especially in those with low CD4 counts. Early and accurate diagnosis of tuberculosis in HIV-positive patients is needed to improve individual treatment outcomes and reduce transmission (19). The

identification of risk factors for TB in HIV-infected people can help refine diagnostic algorithms for tuberculosis screening resulting in earlier detection of active TB and identification of patients eligible for isoniazid preventive therapy. The need for such research is urgent.

1.3. Justification for the study

This patient population used for this study is unusual as it represents a niche sector of the HIV-infected population, distinct from that in either private or public sector health facilities: individuals who elect not to use state facilities but cannot afford to use private health facilities. Studies have sought to identify risk factors of TB in HIV-infected patients and use these to develop clinical diagnostic algorithms to reduce diagnostic delays, costs and TB-related morbidity and mortality (31, 32). Most of these studies have taken place in public sector facilities with potentially very different patient population profiles. There has only been one study published that examined TB prevalence among HIV infected patients enrolling in a fee-for-service health facility in South Africa, as opposed to public sector facilities. This was a prospective study conducted at McCord's Zulu Hospital. a semi-private hospital in Durban, described by Hom et al (33). ZuziMpilo differs from the clinic described in that study because the monthly fee for HIV care at ZuziMpilo is at least four times that paid at McCord's Hospital. The higher ZuziMpilo monthly fee potentially selects for patients in more affluent economic circumstances with possible implications for TB prevalence patterns. Furthermore, the focus of the Durban study was the prevalence of drug

resistant TB and the determination of resistance patterns, rather that the determination of predictors of prevalent TB.

If the ZuziMpilo model of charging a subsidized, all-inclusive monthly fee for HIV care in a private setting proves to be sought-after, acceptable and sustainable, it may be replicated across the country and it will be important to understand TB prevalence patterns and predictors of TB in the populations who seek care in such facilities. This study includes a unique sub-population that differs both from populations that use state facilities and from more wealthy populations with health insurance or medical aid, and determined the prevalence of TB within clients attending the clinic to identify risk factors associated with prevalent TB.

1.4. Literature Review

1.4.1. ***The burden of TB in ART services***

The prevalence of TB/HIV coinfection is highest in the sub-Saharan region of the African continent, ranging from 8.4% in Ethiopia to 77% in Swaziland, in 2011 (2). On the other end of the spectrum, in wealthier regions with low HIV burdens, such as Europe and North America, the risk of incident TB is so low that current guidelines for the management of HIV-infected adults do not recommend routine screening for TB at HAART initiation, although the European guidelines do recommend screening for latent TB infection at the time of HIV diagnosis (34, 35). For instance, in 2011, when the incidence rate for TB was 993 per 100 000 population in South Africa, the TB incidence rates for the entire WHO

region of the Americas, France and Germany were 28, 4.3 and 4.5 per 100 000 population respectively (2). An observational cohort study of 48 854 patients who started HAART between 1996 and 2009, from 12 cohorts in Europe, USA and Canada, found higher rates of AIDS defining events, most commonly TB, in migrants rather than non-migrants. Not unexpectedly, these differences were most marked among migrants from sub-Saharan Africa as opposed to North Africa/Middle East, Latin America and Asia (36). These results, and the results of similar studies, have prompted authors to highlight the importance of screening for TB at HAART initiation in low TB burden countries, especially in migrant populations (36, 37).

The reported prevalence of TB in HIV-infected adults attending outpatient HIV clinics across South Africa varies from 8% to 42.5% (38-44), likely reflecting: different case definitions for prevalent TB used in these studies, varying regional TB prevalence rates, the proportion of TB patients tested for TB, the effectiveness of referral networks between TB and ART services and the thoroughness of pre-HAART TB screening (42). Most studies have reported on the proportion of patients with TB diagnoses at initiation of HAART and include two groups of patients; those who first present to health services with TB and are referred to HAART services after they are tested and diagnosed with HIV and those HIV-positive patients who enroll in HAART services who are diagnosed with TB during preparation for HAART initiation (45).

Table 1.1 summarizes the findings of six South African studies that report estimates of TB prevalence in adults enrolling at dedicated HIV clinics across the country. The prevalence of TB in patients enrolling in HAART services has risen sharply following an intensive

campaign in the public sector to increase provider initiated testing and counselling for HIV (42, 43). In two Cape Town townships, the TB prevalence rose from approximately 23% to 43% between 2001 and 2007 in Kayelitsha (42) and from approximately 16% to 35% between 2002 and 2008 in Gugulethu (43). It is important to note that these areas carry an extremely high burden of TB. In 2003, during the period of retrospective review for both these studies, the annual TB notification rate in Cape Town Metro was 1000/100 000 (46). Yet in the same year, the antenatal HIV seroprevalence rate for the Western Cape province was 13.1%, well below the national average of 28% (47).

Table 1-1: Summary of reported prevalence of TB in HIV-infected adults attending outpatient HIV clinics across South Africa.

Time period and setting	Description of study population and method	Case definition	Proportion with TB	Median CD4 count (all participants)	Reference
April 2004 to March 2007 **Suburban Johannesburg,** Gauteng Province	7,066 HIV-infected adults attending a dedicated HIV clinic at a public sector tertiary hospital Retrospective analysis	Prevalent TB at the time of HAART initiation, including individuals: • already on TB treatment • starting TB treatment concurrently with HAART • Starting TB treatment within 60 days of HAART initiation	23.0% (1628/7066)	**Already on TB treatment:** 59 cells/mm^3 (IQR 23 – 116) **Starting TB treatment and HAART concurrently:** 48 cells/mm^3 (IQR 13 – 112)	Westreich et al, 2009 (39)
May 2001 to December 2007 **Khayelitsha township,** Western Cape • High levels of poverty • High HIV and TB burden	7,323 HIV-infected patients 14 years and older attending 3 public sector primary health clinics Retrospective analysis	Prevalent TB at HAART initiation defined as individuals already on TB treatment	**2001/2002:** 22.7% (65/286) **2007:** 42.5% (789/1860)	**2001/2002:** 42.5 cells/mm^3 (IQR 13 – 95) **2007:** 131 (IQR 64 – 191)	Boulle et al. 2010 (42)

Time period and setting	Description of study population and method	Case definition	Proportion with TB	Median CD4 count (all participants)	Reference
July 2003 to December 2008 **Suburban Soweto,** Gauteng Province	3,456 HIV-infected adults attending a dedicated HIV clinic at a public sector tertiary hospital Retrospective analysis	Prevalent TB at the time of the baseline visit, including individuals: • already on recorded TB treatment • with laboratory confirmation of TB • admitted to hospital with a diagnosis of TB	8% (95% CI 18 – 21)	285 cells/mm^3 (IQR 153 - 452)	Hanrahan et al, 2010 (40)
September 2002 and June 2008 **Gugulethu township**, Western Cape Province • High levels of poverty • High HIV and TB burden	3,770 HAART-naïve adult patients attending a dedicated public sector ART clinic Retrospective analysis	Prevalent TB at time of enrollment into service defined as individuals already receiving TB treatment at time of enrollment.	**September 2002 to June 2005:** 16.0% (95% CI 13.9 - 18.1) **July 2007 to June 2008:** 34.7% (95% CI 31.4 - 38.1)	**September 2002 to June 2005:** 99 cells/mm^3 (IQR 48 – 154) **July 2007 to June 2008:** 120 cells/mm^3 (IQR 56 – 186)	Lawn et al, 2011 (43)
May 2007 to May 2008 **Suburban Durban,** KwaZulu-Natal Province Highest HIV prevalence in the country (37.4% in the province vs. 28.0% in the whole country in 2007)	1,035 HIV-infected adults attending a dedicated HIV clinic semi-private hospital, paying a monthly subsidized fee Prospective cohort study	Prevalent TB at the time of enrollment (HAART initiation) defined as individuals already receiving TB treatment at time of enrollment into study.	18% (191/1035)	78 cells/mm^3 (IQR 40 – 125)	Hom et al, 2012
August 2007 and January 2008 **Urban Klerksdorp and rural surrounds,** North West High HIV prevalence (31.8%)	381 HIV-infected adults referred for HAART initiation to a dedicated HIV clinic at a public sector hospital. Prospective cohort study	Prevalence of TB at the time of enrollment into study (HAART initiation), or within 3 months of enrollment, defined as: Compatible clinical or radiological features of TB with: ●Laboratory confirmation of *M. tuberculosis*, or	32% (95% CI 26.8 – 36.6)	120 cells/mm^3 (IQR 72 – 168)	Hanifa et al, 2012 (44)

Time period and setting	Description of study population and method	Case definition	Proportion with TB	Median CD4 count (all participants)	Reference
		• No laboratory confirmation and clinical improvement after 2 months of anti-tuberculosis treatment and no other cause of disease found *Patients taking anti-tuberculosis treatment at the time of enrollment or within the previous three months were excluded.*			

Analysis of 7066 patients attending a large public sector HIV clinic in Johannesburg revealed a prevalence of TB in patients initiating HAART of 23.04% (95% CI 22.06 – 24.04). The definition of prevalent TB included individuals already on TB treatment at the time of HAART initiation, those starting TB treatment concurrently with HAART and those newly diagnosed within 60 days of HAART initiation (39). In a study that explored the association between body mass index (BMI) and the risk of tuberculosis and death at a Soweto HIV clinic, the baseline prevalence of TB in a cohort of 3456 HIV-infected adults was 8% (95% CI 18 – 21) (40). The case definition of TB in this study included individuals with laboratory confirmed TB, recorded initiation of TB treatment or hospitalisation with a diagnosis of TB. In a prospective cohort study designed to investigate the prevalence of, and evaluate screening modalities for, undiagnosed TB in HAART-eligible adult patients referred to an HIV clinic at a public sector hospital in Klerksdorp in the North West province, the prevalence of undiagnosed active TB at enrollment or within 3 months after enrollment was 32% (95% CI 26.8 – 36.6) (33). In this study the case

definition for prevalent TB was tighter than those used for the other studies quoted. Patients were classified as having TB if they had compatible symptoms and signs of TB and *M. tuberculosis* cultured from any site (definite TB), compatible symptoms and signs of TB and other laboratory evidence for TB (Probable TB) or compatible symptoms and signs of TB, no laboratory evidence for TB and clinical improvement after two months of TB treatment (Possible TB). Because the focus of the study was undiagnosed TB, all patients already on TB treatment at the time of enrollment, and those who had been on TB treatment within the previous three months, were excluded. The last mentioned study was conducted in a dedicated HIV clinic at a semiprivate hospital serving a primarily urban population in Durban, KwaZulu-Natal. This study site was unique among the 5 studies referenced in that the clinic in question charged a subsidized fee for service which, during the study period, amounted to an all-inclusive monthly fee of ZAR90. This was a cross-sectional cohort study designed to estimate the prevalence of drug-resistant TB and describe resistance patterns in adults starting HAART. Of the 1035 patients recruited, 20% (210) were already on TB treatment at the time of enrollment and 18% (191) were sputum positive for *M. tuberculosis*. Table 1.1 highlights an important association between the median CD4 counts of the study populations and the estimates of TB prevalence, evident despite the varying case definitions used to define TB prevalence. The study that reports the lowest by far prevalence also reports the highest, by far, median CD4 count. The median CD4 count for the study at a non-fee paying HIV Wellness clinic at a tertiary public sector hospital in Soweto was 285 cells/mm^3 (IQR 153 – 452). In comparison, the other four studies, conducted in Kayelitsha, Gugulethu, Johannesburg and Durban reported median CD4

counts that range from 42 to 131 cells/mm^3 and TB prevalence rates that range from 16% to 43%.

Mozambique and Zambia had similar TB/HIV coinfection rates to South Africa in 2011, 63%, 64% and 65% respectively (2). In both countries, studies have reported a TB prevalence of approximately 11% among HIV-infected adults initiating HAART between 2004 and 2006 and from 2004 to 2005 respectively (48, 49). In marked contrast, the HIV/TB coinfection rate in Burkina Faso to the north was 17% (2). Not surprisingly, the incidence of TB in the months following HAART initiation are much lower than one would expect from the countries further south with far higher levels of TB/HIV coinfection. In a retrospective study that included 2383 HIV-infected adults initiating HAART in four different HIV treatment centres, 96% of HIV positive patients were still on HAART and free of TB at the end of the first year of follow-up (50).

1.4.2. ***Risk factors for TB***

Poverty, overcrowded dwellings, poorly ventilated workplaces, poor nutrition, and lack of access to quality health care are well-recognized drivers of TB transmission and are thought to be similarly important for HIV-associated TB (6, 51). These are features of slum life to which increasing numbers of South Africans are exposed as the population urbanizes rapidly without concomitant economic development and prosperity (52). A study published in 2007, based on an analysis of 13,043 Demographic Health Survey (1998) respondents, examined the demographic and behavioural risk factors for prevalent TB in the general population. Cigarette smoking, alcohol consumption, low body mass index (BMI), a lower level of personal education, unemployment, and lower household wealth were associated

with statistically significant increased odds of a diagnosis of TB (53). It is unlikely that people who seek care at ZuziMpilo, a fee-for-service health facility, are as exposed to the poor socio-economic factors as those with no other choice but to use public-sector health facilities.

Studies of risk factors for TB in HIV-infected people have identified advanced immunodeficiency (low CD4 cell count and WHO Clinical Stage 3 or 4) and high plasma viral load as the most important risk factors associated with both prevalent and incident TB (38, 39, 41, 54, 55). Unlike in HIV seronegative populations, the prevalence of TB appeared not to change with increasing age in three large South African cohorts of adults attending large state-run HIV services (38, 39, 41, 54, 55). However, a recent analysis of NHLS data from 2004 to 2012 showed that there was a significant difference in the incidence of microbiologically confirmed TB across broad age categories; the highest rates were seen in the 25 to 44 year old age groups (14).

In many populations, the prevalence of TB in men and women differs across different age groups, with an excess TB risk in young women and old men. (56, 57) However, overall, in most regions of the world, adult men are more likely to develop active TB than adult women (58). Globally in 2011, the male-to-female ratio of case notifications of new smear positive cases was 1.7 and in South Africa it was 1.3 (2). This gender difference persists even in large, systematic epidemiological studies that take into account potential confounders that could influence case notification rates, such as differential health seeking behaviours, access to health care services, exposure to smoking, alcohol and mine dusts and

other pollutants, etc. (58). For example, a three-country case-control study in West Africa published in 2005 and a household survey of more than 260,00 individuals in Bangladesh published in 2004 confirmed male sex as a risk factor for TB, independent of socioeconomic, environmental, cultural and host-related potential confounding factors (59, 60). In a recent study in the Western Cape of South Africa, male sex was an independent predictor of latent TB infection among adolescents in a high TB burden area (61). In this study, the prevalence of HIV was not measured but was expected to be low, reflecting the low (5 to 10%) annual antenatal HIV seroprevalence estimates for the area (relative to the much higher (30%) national antenatal seroprevalence. Several other studies in South Africa have picked up the similar sex difference among HIV-infected adults. Male sex was found to be a significant independent predictor of TB prevalence at the time of HAART initiation in two large cohorts (7000 and 3770 respectively) attending public sector HIV clinics in Johannesburg and Gugulethu township, Cape Town (41, 43). Similarly, male sex was an independent risk factor for a baseline history of TB at HAART initiation in a prospective cohort of 1771 members (and their dependents) of the South African National Defence Force attending military HAART services (38, 54, 55).

A previous history of TB has been found to be partially protective for prevalent TB at the time of HAART initiation, the more recent the episode, the greater the protection, in two of the studies mentioned above, both the Johannesburg and Gugulethu cohorts (39, 41, 54)

There is a great deal of evidence for low BMI as a predictor of disease progression and mortality among HIV infected adults (62-64) and by inference, for tuberculosis which is the

leading cause of death among those living with HIV in Africa (65). There is also strong evidence for a direct relationship between increasing BMI and reduced risk for tuberculosis. In a cohort study of 3635 HIV-infected adults in a Soweto HIV wellness clinic, high BMI (specifically overweight and obese BMI) was shown to be strongly protective against incident TB and all-cause mortality, after adjusting for CD4 cell count and HAART use (40). Similarly, underweight BMI was identified as an independent risk factor for prevalent TB in this Johannesburg cohort (41) and in a Ugandan study (66). Unemployment was identified a risk factor for prevalent TB in the Gugulethu cohort (41).

HAART is strongly associated with a marked reduction in TB incidence in adults with HIV across all CD4 counts (45, 67-69). This response is dependent on the duration of treatment. Within the first 6 to 12 months after HAART initiation the risk for TB diminishes rapidly, mirroring the magnitude of immune recovery as reflected in rising CD4 counts. A large cohort study in a Cape Town township in South Africa, examined TB incidence stratified by serially updated CD4 counts during HAART and compared TB incidence during early (< 4 months) and long term (> 4 months) HAART. The study revealed a strong, graded, independent association between TB risk and updated CD4 counts; the adjusted TB rate associated with the lowest CD4 stratum, <100 cells/mm^3, was more than nine-fold greater than the rate associated with the highest stratum, >500cells/mm3 (70). The study also documented a now well-established finding that TB incidence remains exceptionally high in the first months after initiating HAART, even after adjusting for CD4 count and viral load. Among patients with CD4 cell counts < 200 cells/mm^3, there was a 1.7-fold excess adjusted TB incidence rate during early HAART compared with during long-term

treatment. The study suggests that much of the TB burden in the first few months after HAART initiation is due to the "unmasking" of asymptomatic or minimally symptomatic disease that was present on initiation of HAART but missed during screening (45). This phenomenon, known as the immune reconstitution inflammatory syndrome (IRIS), occurs when rapid restoration of pathogen-specific immune responses causes either the paradoxical deterioration of a treated infection or triggers the new and often florid presentation of previously subclinical infection (71). IRIS occurs in 10 – 27% of patients initiating HAART and typically occurs in the first few months after initiation (72).

Unfortunately, multiple studies have observed that, despite the steady decline with long term HAART, TB incidence remains elevated relative to the background incidence seen in the general population, despite many years of HAART therapy (67, 70).

1.5. Study Objectives

1.5.1. ***Overall objective***

To determine the prevalence of TB, and identify factors associated with prevalent TB in HIV-infected adults attending ZuziMpilo.

1.5.2. ***Specific objectives***

- To describe the characteristics at enrolment of the study population represented by all those who attended ZuziMpilo in the period from August 2009 to December 2011, including demographic, socio-economic status and anthropometric variables as well as variables indicating HIV disease progression and substance use history.

- To determine the proportion of HIV-infected adults with prevalent TB at enrolment in those who attended ZuziMpilo in the study period.
- To investigate whether any of the characteristics mentioned above independently predict prevalent TB in this population.

2. MATERIALS AND METHODS

This chapter describes the study design, the study population and selection of the study sample, the data sources mined, definitions of outcome and exposure variables, the statistical methods employed to analyse the data and ethical considerations.

2.1. Study design

This was a cross sectional, secondary analysis of data extracted from the routine electronic medical records of HIV-infected adults who attended ZuziMpilo from August 2009 to December 2011.

2.2. Study setting

The ZuziMpilo Medical Centre (ZuziMpilo) is a private clinic in downtown Johannesburg - at the time of the study funded by the Presidents Emergency Plan for AIDS Relief (PEPFAR) - that offers fee-for-service health care for people living with HIV. It was conceived by the Perinatal HIV Research Unit in 2006 to fill the gap between public and private sector HIV care. ZuziMpilo is targeted primarily at employed adults without medical aids who prefer not to use state health facilities (73).

ZuziMpilo offers voluntary counselling and testing for HIV, a wellness programme that caters for HIV-infected people who are not yet eligible for HAART and antiretroviral treatment. Symptom-based TB screening with immediate investigation of those who have

symptoms, onsite TB therapy initiation and referral to public-sector facilities for ongoing TB therapy, and monitoring for clinical response to TB therapy are standard of care services offered to HIV-infected patients at ZuziMpilo. During the study period, ZuziMpilo charged patients an all-inclusive monthly fee for their care that increased from ZAR430 in August 2009 to ZAR600 in December 2011 (74).

ZuziMpilo is situated in the densely populated Johannesburg inner city. According to the Community Survey conducted in 2007, the population of the City of Johannesburg Metropolitan Municipality as a whole was 3,888,180 (75). In the inner city alone, some 248 599 residents live in 97 484 households and around 1 million commuters enter the inner city every day. In 2009, the average household monthly income of inner city residents was approximately R6, 389.10 (76). The antenatal HIV seroprevalence in the City of Johannesburg Municipality was 29.6% in 2010, close to the Gauteng provincial and national prevalence estimates (30.4% and 30.2% respectively) (77). In the same year, the annual incidence rate for all types of TB in the Municipality was 630 per 100 000, below the national average of 805 per 100 000.

2.3. Study sample

The study sample was selected based on non-random sampling including all HIV-infected adults, 18 years and older, who were enrolled consecutively into care at ZuziMpilo in the 28 months, from 1 August 2009 to 31 December 2011. Although ZuziMpilo started enrolling patients into care from 2006, August 2009 was selected as the start of the study period because from this date it became standard procedure to collect detailed baseline

information from patients. Thus, for patients enrolled since the beginning of August 2009, there is additional data related to a range of characteristics including; occupation, income, education, medical aid membership, financing of medical care, alcohol and tobacco use.

2.4. Data source

The data used from this study were those collected for routine medical care; they were not collected for research purposes. ZuziMpilo uses TherapyEdge^{TM}, an HIV-specific rapid data collection system or electronic medical record, to capture patient data electronically in real-time during consultations. Information about a patient may be collected by at least three different staff members at each visit:

1. At the initial visit, an **administrative clerk** collects socio-demographic and referral data and completes a survey that collects information that includes: previous exposure to antiretroviral treatment, alcohol use and smoking, employment, monthly all source-income, monthly cell phone expenditure, medical aid membership, financing of care at ZuziMpilo and how the patient came to know about ZuziMpilo.
2. A **nurse** captures information about: past medical and surgical history and symptoms and enters height and weight measurements if done.
3. Finally, a **doctor** captures information relating to: additional medical history, the clinical examination findings, diagnosis and treatment.

Most blood tests results are automatically entered into TherapyEdge^{TM} by the laboratory staff.

It is standard procedure at the clinic to screen all HIV-infected patients at their first visits, and regularly thereafter, for symptoms and signs of TB using a simple questionnaire and a physical examination. According to standard operating procedure, three consecutive sputum samples for acid-fast bacilli microscopy and culture should be collected for those with suspected TB. Patients are referred offsite for additional diagnostic tests, such as chest radiography and mycobacterial evaluation of cerebrospinal fluid, pleural fluid and lymph node biopsy specimens, as indicated. Patients diagnosed with TB are registered, initiated on TB treatment and referred to state TB services for notification and treatment continuation. Patients on TB treatment remain in care at ZuziMpilo and are monitored for clinical improvement.

2.5. Definitions

Definitions of study variables were established *a priori* - before the data was analysed. Table 2.1 below summarises the nature of each variable.

2.5.1. ***Exposure variables***

We were interested in risk factors for prevalent TB. Therefore, the values selected for these variables, such as WHO Clinical Stage, height and weight, and CD4 count, etc, were the nearest measurement to the date of the first visit and for the purposes of this study were restricted to within 60 days prior to, or following, the date of the first ZuziMpilo visit.

- **Baseline BMI** - calculated from the measurements for height and weight (BMI=height cm /weight (kg) squared) taken on the visits nearest to the first visit date and falling

within a period of 60 days prior to and post the first visit date. Baseline BMI was stratified into 4 categories based on the World Health Organization classification of adult BMI: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–25 kg/m^2), overweight (BMI 25.1–30 kg/m^2) and obese (BMI >30 kg/m^2) (78).

- **Baseline CD4 cell count (cells/mm3)** - defined as the value nearest to the first visit date and within a period of 60 days prior to, or following, the first visit date. CD4 count was stratified into the following categories: < 200 cells/mm^3, 200 – 349 cells/mm^3 and > 350 cells/mm^3.
- **WHO Clinical Stage** (1) – the value for this parameter was taken from the visit nearest to the first visit date and falling within a period of 60 days prior to, or following, the first visit date. WHO Clinical Stage was categorized into Stage 1 - 4.
- **HAART status** – defined as whether the participant had previous or current exposure to HAART or not and categorised as follows: HAART naïve or has started HAART.
- **Period of exposure to HAART** – defined as the number of completed months that the participant had ever taken combination antiretroviral therapy at the first visit date.
- **Smoking history** – defined as the self-reported number of cigarettes or pipes that the participant smoked per week, self reported at the time of the first visit.
- **Alcohol history** - defined as the self-reported number of alcoholic drinks the participant consumes per week at the time of the first visit.
- **Level of education** – defined as the highest level of education attended and categorised into 3 categories; primary school, secondary school and tertiary education.

- **Employment** – defined as the participant's most recent (within the past year) or current employment history and was categorised as follows: unemployed, full-time employed, self-employed, part-time jobs, student and pensioner.
- **Source of knowledge about ZuziMpilo** – defined as the source of the information when the participant heard about ZuziMpilo for the first time, with 5 categories as follows; partner, family or friend, employer or workplace, health worker or health facility, mass media and internet.
- **Health insurance** – defined as whether the participant had health insurance or medical aid at the time of the first visit or not.
- **Monthly all-source income** – defined as average monthly income from any source and was categorised into 3 categories; less than R1,000/month, R1,000 -R4,999/month and R5,000 or more/month.
- **Monthly cell phone expenditure** – this was categorised into 2 categories: zero cell phone expenditure - R200/month, and >R200/month. Monthly cell phone expenditure was used as proxy for disposable income.
- **Source of payment for care** – defined as person responsible for payment to ZuziMpilo; and divided into two categories: self-funded and funded by another person.

*2.5.2. **The outcome variable***

The outcome of interest was prevalent TB. Prevalence was defined in relation to the first visit date. A diagnosis of prevalent TB, as opposed to incident TB, was defined as a diagnosis of TB made:

- Within 91 days prior to the first visit to ZuziMpilo or
- At the first visit
- Within 61 days following the first visit

The rationale for this time frame is as follows: Selecting patients diagnosed within a 91 day window prior to the first visit identifies "current" TB episodes and excludes "previous" diagnoses and patients who would most likely already have rising CD4 counts in response to TB treatment. Selecting patients diagnosed within a 61 day window after the first visit identifies patients who most likely had TB disease that was missed during enrolment screening.

Participants diagnosed with prevalent TB were then classified into one of five diagnostic categories as follows (79):

- **Culture confirmed TB;** defined as the presence of clinical signs and symptoms of tuberculosis and a positive culture for *Mycobacterium tuberculosis* from any site.
- **Probable TB;** defined as the presence of clinical signs and symptoms with acid-fast bacilli on a sputum smear or caseous necrosis in a tissue-biopsy specimen.
- **Possible TB;** defined as the presence of clinical signs and symptoms without microbiological or histological evidence of *M. tuberculosis* but with a documented clinical response to antituberculosis therapy (e.g. symptoms diminishing and/or increase in weight)
- **Suspected TB;** defined as the presence of clinical signs and symptoms without microbiological or histological evidence of *M. tuberculosis* and without documentation of a clinical response to antituberculosis therapy.

- **Not TB;** defined as the presence of clinical signs and symptoms of tuberculosis without microbiological or histological evidence of *M. tuberculosis* but with microbiological evidence of alternative mycobacterial species, for example, M. avium complex.

Hard copy and electronic clinical records were searched for the evidence needed to classify cases as above, including laboratory reports and data from subsequent visits that indicated the presence or absence of a clinical response to TB treatment. If no laboratory reports could be found in the clinical records, the National Health Laboratory Service database was scrutinized for any evidence of a laboratory diagnosis of TB (microbiology, histology and cytology reports).

It was anticipated that there might be several patients who would remain classified as having "Suspected TB", despite considerable efforts to mine source documents and local laboratories for information that would allow them to be included in the study case definition. Such patients were excluded from the study definition. This approach is similar to the case definition used in a recently published prospective cohort study, conducted by Hanifa et al, to determine the prevalence of previously undiagnosed TB among ART-eligible adults at a public sector hospital HIV clinic in Klerksdorp, Gauteng Province. (44)

Table 2-1: **Summary of the outcome and exposure variables**

Variable	Coding
Prevalent TB	0 = Not diagnosed with prevalent TB or diagnosed with TB and classified as Suspected TB or Not TB 1 = Diagnosed with TB and classified as Confirmed TB, Probable TB or Possible TB
Age (in completed years)	The difference between the date of birth and the date of the first visit
Sex	1 = Male 2 = Female
BMI (kg/m2)	Categorized according to the WHO International Classification of Adult BMI: 1 = Underweight (BMI <18.5) 2 = Normal (BMI 18.5–25)

Variable	Coding
	3 = Overweight (BMI 25.1–30) 4 = Obese (BMI >30)
WHO Clinical Stage	1 = WHO Stage 1 2 = WHO Stage 2 3 = WHO Stage 3 4 = WHO Stage 4
CD4 cell count (cells/mm^3)	1 = < 200 2 = 200 – 349 3 = >350
Months on HAART	1 = HAART naive 2 = HAART for < 6 completed months 3 = HAART for> 6 months
History of current smoking	1 = No smoking 2 = < 7 cigarettes/week 3 = ≥ 7 cigarettes/week
History of current alcohol use	1 = No alcohol 2 = < 6 drinks/week 3 = ≥ 6 drinks/week
Highest level of education achieved	1 = Primary school 2 = Secondary school 3 = Tertiary education
Employment status	1 = Unemployed 2 = Not unemployed (includes the formally employed, self-employed, pensioners and students)
Monthly all-source income	1 = < R1,000 2 = R1,000 – R4,999 3 = > R5,000
Monthly cell phone expenditure	1 = R0 to R200 2 = >R200
Medical aid membership	0 = No 1 = Yes
Source of payment for consultations	1 = Self 2 = Funded by other
Source of knowledge about ZuziMpilo	1 = Workplace 2 = Health facility 3 = Mass media 4 = Partner, family or friend

NOTE: Some categories were defined by TherapyEdge ™ electronic record.

2.6. Data Analysis

2.6.1. ***Data preparation and cleaning***

TherapyEdgeTM (v. 3.2, TherapyEdge Inc, Massachusetts, USA) data is stored in a MySQL database. ZuziMpilo data for the study period was exported in eight comma separated value (CSV) files. The CSV files were imported into STATA (STATA Statistical Analysis package, v. 11.0; College Station, Texas, USA), via MS Excel, for coding, cleaning, merging and statistical analysis. The export of the main demographic questionnaire was not in tabular format but contained a list of questions, unique patient identifiers and responses in text format. This file was converted using a Python (v. 2.6; Beaverton, USA) script and Python dictionaries to convert the file into a usable CSV file. Using a document that outlines the TherapyEdge database structure (80), it was possible to merge multiple files using unique linking variables.

TherapyEdge^{TM} was not designed primarily as a research data capture tool and, despite the numerous logical and range checks designed to facilitate accurate and complete data entry, implausible and missing values presented significant analytical obstacles. The dataset was screened for duplicated observations which were removed and missing and inconsistent values. Range checks, box and whisker plots and histograms were used to identify outliers, implausible values and unexpected distributions with continuous variables. An attempt was made to decrease the number of missing values and obtain valid values for variables with implausible values by manually checking source documents at ZuziMpilo - clinical and laboratory records - both electronic and hard copies of source documents. Additionally, for

certain clinical variables, for example; height and weight for BMI calculation, CD4 count and WHO Clinical Stage, the value from the visit closest in time and within a defined time limit (appropriate to the variable in question) of the first visit date. Clearly implausible values were recorded as missing when the above data validation measures were unsuccessful.

2.6.2. ***Descriptive statistics***

The study population was described in terms of age, gender, BMI, baseline CD4 cell count, WHO Clinical Stage, exposure to HAART, occupational status, monthly income, cell phone expenditure, medical aid membership, smoking history, alcohol history. The mean and standard deviation, or the median with its interquartile range were used to summarise continuous variables for normal or non-normally distributed data respectively. Frequencies (n) and percentages (%) were used for categorical variables. The overall prevalence of TB was reported with its 95% confidence intervals (95% CI) and then for subcategories of patients.

2.6.3. ***Inferential statistics***

Each of the variables was tested for association with prevalent TB, using the two sample t-test for the means of continuous variables and the Pearson's chi-square test for the frequency and distribution of categorical variables and univariate logistic regression. Any variable with a P value < 0.20 in the univariate analysis was included in the multiple

variable regression model, as well as those with $p > 0.20$ that had biological plausibility for and established importance as predictors of TB in the literature. Adjusted Odds Ratios (aORs) with $p > 0.050$ were considered not statistically significant in the multivariable analysis. Interaction terms were introduced into the model to explore effect modification and confounding.

To ensure that the final regression model satisfied the assumptions of logistic regression and produced valid statistical inferences, the model was subjected to diagnostic tests to evaluate the model for specification error (*linktest*), how well the model fitted the data (log likelihood chi-square and pseudo R-square Hosmer and Lemeshow's goodness-of-fit test), multicollinearity between exposure variables (*collin*), the presence of influential points and the extent of the influence of these influential points on the regression equation (81).
Statistical significance was set at 0.05 (two tailed).

2.6.3.1. Dealing with missing variables

Missing data may bias conclusions about the size and existence of associations between the outcome variable and exposure variables (82). In this study, missing data was a consequence of information not gathered or evaluations not performed during visits, patient non-attendance of visits and the recoding of implausible values as missing. Analysis of missing values using Chi-squared tests was done to investigate whether missing data were associated with the outcome (Prevalent TB) and is presented in Appendix 6.1. In addition to the above analysis, all analyses exploring associations between exposure variables and the

outcome of interest were conducted using two different datasets, one that assigned a unique category for missing values within each variable and one that did not. This allowed for assessment of systematic differences between the datasets in the bivariate and univariate regression analysis. In the final multivariable regression models, the dataset that assigned unique categories to missing values was used to prevent the exclusion of individuals from the model who had missing values for any variables.

2.6.3.2. Testing the validity of the study case definition

A sensitivity analysis to explore the effect of excluding patients classified as having "Suspected TB" from the study case definition was carried out. This alternative analysis included these patients in the study case definition for prevalent TB. The results are displayed in Appendix 6.2.

2.7. Sample size

A sample size of 1800 was assumed to evaluate the adequacy of the study sample based on the total of 1967 individuals enrolled into care at ZuziMpilo during the period 1 August 2009 to 31 December 2011 (29 months), allowing for the exclusion of children under 18 years of age. The reported TB prevalence for public sector HIV clinics in Johannesburg ranges from 8% to 20% (39, 40). With respect to the precision of the measure of TB prevalence in a sample of 1800, with an estimated TB prevalence at enrolment in the study population assumed to be 10% (towards the lower estimate in the range of reported

prevalence), would enable a point estimate of TB prevalence with its 95% confidence intervals of 1.2% (absolute) on either side of this estimate.

With respect to identification of predictors of prevalent TB, exposure to HAART is used as an example. Assuming that 80% of participants were not yet on HAART (the exposure) at their first ZuziMpilo visit, and assuming that the prevalence of TB in the unexposed group is 10%, with a sample size of 1800, this study will be powered at 80% to detect an odds ratio of 1.72. Thus a sample size of at least 1 800 will be sufficient to carry out the proposed descriptive and inferential statistics at the stated significance and power levels.

2.8. Ethical considerations

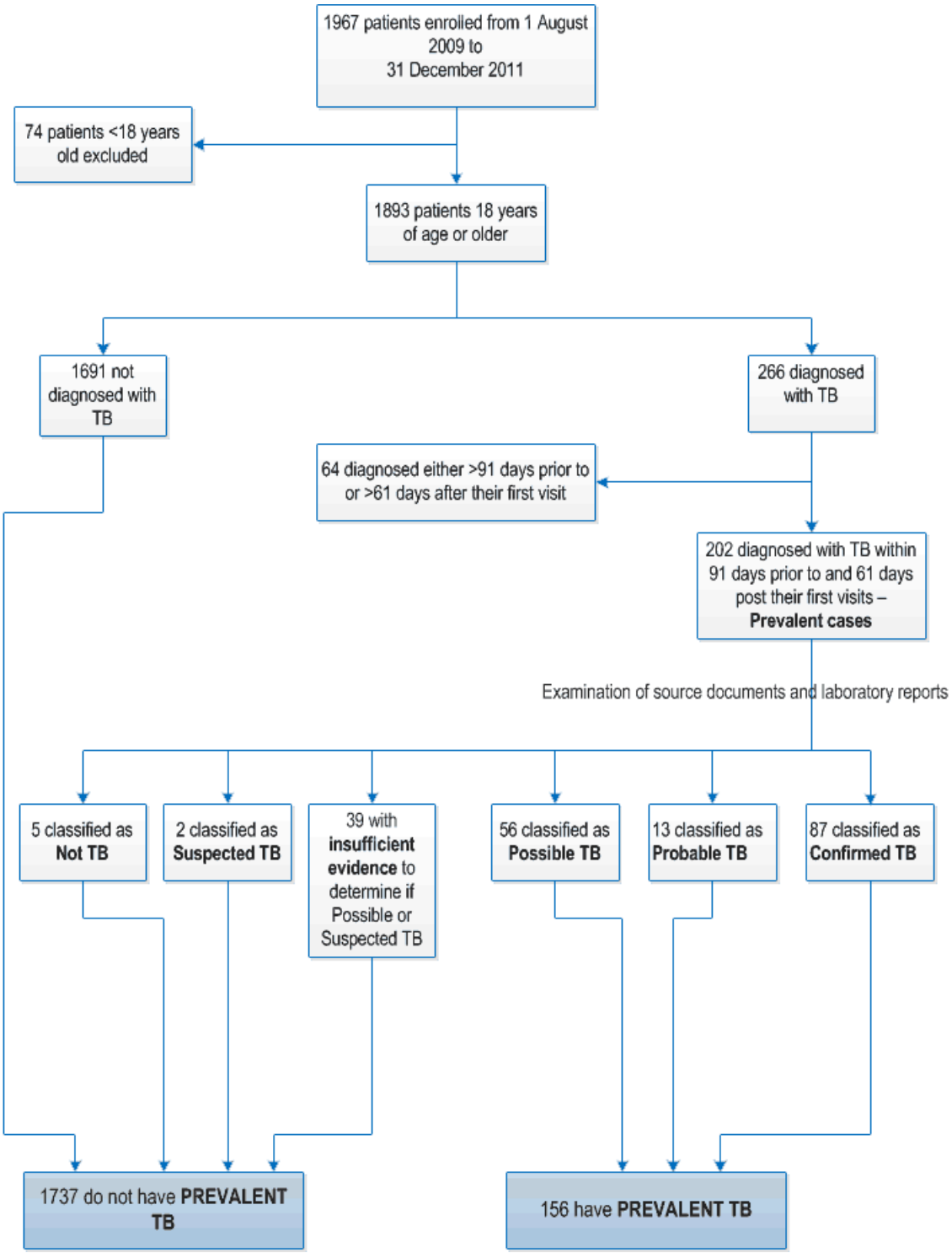
Patients at ZuziMpilo give signed informed consent at their first visit, using a generic form approved by the University of the Witwatersrand's Human Research Ethics Committee (Medical), for their data to be used for research (Clearance certificate number: M070361), see Appendix 3. Participant confidentiality was protected by removing unique numeric identifiers and personal identifiers from the dataset prior to analysis. This was a retrospective record review and the study posed minimal risk to clients of ZuziMpilo. The Postgraduate Committee and the Human Research Ethics Committee, Faculty of Health Sciences, University of Witwatersrand approved this analysis (Clearance certificate number: M10M101177), see Appendix 6.5.

3. **RESULTS**

During the period between 1 August 2009 and 31 December 2011 (29 months), 1967 individuals were enrolled into care at ZuziMpilo. Seventy-four patients younger than 18 years old were excluded, yielding a final dataset of 1893 individuals of 18 years or older.

Of the 266 patients diagnosed with TB during the study period, 202 (75.9%) met study criteria for a prevalent TB as opposed to an incident TB diagnosis. Of these 202 patients, 26 (13.3%) were diagnosed within 91 days prior to their first clinic visit, 30 (15.4%) were diagnosed at their first clinic visit and 139 (71.38%) were diagnosed within 61 days after their first clinic visit. Detailed examination of source documents (laboratory data and clinical records) to classify TB cases in terms of the study case definition of prevalent TB showed that 156 patients fulfilled the study definition for TB, yielding an overall TB prevalence at enrollment of 8.24% (95% Confidence Interval (CI) 7.04 – 9.57). Figure 3.1 below illustrates the inclusion of patients in the study sample and their classification in terms of the study outcome, Prevalent TB.

Figure 3-1: Flow chart illustrating the inclusion of patients in the study sample and the classification in terms of the study outcome, Prevalent TB



For 39 patients who had been diagnosed with TB, there was insufficient evidence for a definitive classification as either "Possible TB" or "Suspected TB". Of these 39 patients, 14 had subsequent visits but not within the period of 25 to 70 days post the date of diagnosis which is the time period within which clinical improvement could have been assessed. Three were transferred out and three died, at 14, 18 and 23 days after diagnosis respectively. These patients were excluded as Prevalent TB cases.

Table 3.1 shows the timing of the various classifications of TB diagnoses. The majority of patients with study-defined prevalent TB were diagnosed with TB at ZuziMpilo (84.6%), either at the first visit (12.2%) or within 61 days thereafter (72.4%). Just above 15% were diagnosed before referral to ZuziMpilo. Almost all (95.9%) of the 39 patients for whom there was insufficient evidence for classification with respect to the study definition of prevalent TB were diagnosed empirically at ZuziMpilo.

Table 3-1: The timing of TB diagnoses of patients within various diagnostic classifications.

Classification	TB diagnosed before referral	TB diagnosed at 1st visit	TB diagnosed after first visit
Confirmed TB (%)	4 (2.56)	7 (4.49)	76 (48.72)
Probable TB (%)	3 (1.92)	2 (1.28)	8 (5.13)
Possible TB (%)	17 (10.90)	10 (6.41)	29 (18.59)
Total with TB (%)	**24 (15.38)**	**19 (12.18)**	**113 (72.14)**
Insufficient evidence for TB diagnosis (%)	2 (5.13)	11 (28.21)	26 (66.67)

3.1. Analysis of missing values

There were no missing values for the variables “Age”, “Sex” and “Time on HAART”. The variable which has the highest proportion of missing values was “WHO Clinical Stage” with 823 missing values (43.48%). For all remaining variables included in the database, the proportion of missing values was below 20%. Table 3.1 presents the characteristics of the overall study sample and includes the number and proportion of missing values for each exposure variable. Missing data were associated with prevalent TB for the variables “WHO Clinical Stage” and “BMI”. For “WHO Clinical Stage”, patients for whom a value for WHO Stage had been recorded had a significantly higher prevalence of TB than patients with missing values for WHO Stage ($P < 0.050$). Similarly, for “BMI”, patients for whom both height and weight were recorded had a significantly higher prevalence of TB than patients with missing values ($P < 0.050$).

The data presented in this chapter derives from analysis conducted using a dataset that assigned missing values a unique category in each variable. A sensitivity analysis was conducted using a dataset that did not include missing values in a separate category for each variable. The results for the contingency analysis and univariate logistic regression were comparable with respect to the direction and magnitude of the associations.

3.2. Description of the patient population

3.2.1. ***Demographic characteristics***

The median age of the 1893 patients was 32 years (IQR 26 - 38) and 60.2% were women. The median age of women (30 years [IQR 25 – 37]) was significantly younger ($p < 0.000$) than that of men (34 years [IQR 29 – 40]). The majority of patients were Black Africans (91.8%) with other ethnic groups; Whites, Coloureds and those classified as "Other", each representing less than 1% of the patient population.

3.2.2. ***Clinical characteristics, HIV disease progression indicators, and tobacco and alcohol consumption history***

At enrollment, over a third (37.8%) of all individuals had normal BMIs, over a third (36.6%) were obese or overweight and 8.3% were underweight. Significantly more ($p < 0.000$) women were obese or overweight than men; 16.9% of women compared to 5.7% of men were obese ($p < 0.000$) and 25.3% of women compared to 22.4% of men were categorized as overweight. Approximately a fifth (21.5%) of patients was classified as WHO Clinical Stage 3 or 4. Overall, the median CD4 count was 239 cells/mm^3 (IQR 110 – 405) and 38.8% of patients had profound immunosuppression with a CD4 count < 200 cells/mm^3). The majority of patients (83.4%) were HAART naïve and 16.6% had already started HAART prior to their first visits to ZuziMpilo. Of those who had started HAART prior to enrollment at ZuziMpilo, the majority (74.0%) had been on HAART for more than

6 months. The majority (86.5%) of patients with an enrollment CD4 count below 200 cells/mm^3 had not yet started HAART ($p < 0.000$).

3.2.3. ***Socioeconomic, educational and other characteristics***

Over half the sample population (57.4%) had reached tertiary education (partial or complete), 28.4% had received secondary education level and 8.0% had received primary education. The majority of patients (75.0%) was employed or had income in the form of pensions or support while studying while a fifth (20.9%) were unemployed. Approximately a fifth, (21.6%) earned less than R1000 a month from all sources, 31.7% earned between R1000 and R5000 a month and 28.8% earned more than R5000 a month. Just under two thirds (63.4%), reported spending less than R200/month on cell phone/s. The majority of patients (73.3%) did not have health insurance and, at enrollment, most patients (69.5%) at ZuziMpilo made out-of-pocket payments while the cost of care for 204 individuals (10.8%) was paid for by someone other than themselves (employer, family member, friend, etc.). Patients were most likely to have heard about ZuziMpilo from a partner, family member or friend (28.8%), the mass media (25.2%) or a health facility (24.0%) than from the workplace (2.8%).

Table 3-2: Characteristics of adult HIV-infected patients enrolled at ZuziMpilo Medical Centre from 1 August 2009 to 31 December 2011

Characteristic		
	Median	**IQR**
Age (median, IQR)	32	26 - 38
CD4 count (median, IQR)	239	110 - 405
	N	**%**
Sex		
Male	1140	60.22
Female	753	39.78
Ethnicity		
Black	1737	91.76
Coloured	16	0.85
White	12	0.63
Other	3	0.16
Missing	125	6.6
BMI		
Obese	236	12.47
Overweight	457	24.14
Normal weight	715	37.77
Underweight	155	8.19
Missing	330	17.43
WHO stage		
Stage 1	288	15.21
Stage 2	375	19.81
Stage 3	272	14.37
Stage 4	135	7.13
Missing	823	43.48
CD4 count		
>350	553	29.21
201 to 350	463	24.46
<200	734	38.77
Missing	143	7.55
HAART Status		
Not on ART	1578	83.36
Started ART	315	16.64
Months on HAART		

Characteristic		
HAART naive	1578	83.36
HAART < 6 months	82	4.33
HAART > 6 months	233	12.31
Smoking		
No smoking	1587	83.84
≤7 cigarettes/week	114	6.02
>7 cigarettes/week	85	4.49
Missing	107	5.65
Alcohol use		
No alcohol	1371	72.42
<6 drinks/week	237	12.52
≥6 drinks/week	137	7.24
Missing	148	7.82
Level of education		
Primary school	152	8.03
Secondary school	537	28.37
Tertiary education	1086	57.37
Missing	118	6.23
Employment status		
Unemployed	1418	74.91
Not unemployed[Π]	394	20.81
Missing	81	4.28
Monthly income		
< R1,000	409	21.61
R1,000 to R4,999	600	31.7
> R5,000	546	28.84
Missing	338	17.86
R0 to R200	1200	63.39
>R200	335	17.7
Missing	358	18.91
Medical Aid		
Has medical aid	174	9.19
No medical aid	1387	73.27
Missing	332	17.54
Financing of care		
Self-funded	1315	69.47
Funded by other	204	10.78
Missing	374	19.76

Characteristic		
Knowledge of service		
Workplace	52	2.75
Health facility	454	23.98
Mass media	476	25.15
Partner, family or friend	545	28.79
Missing	366	19.33

Π Not unemployed = employed (full-time, part-time and self-employed), pensioners and students

3.3. Associations between patient characteristics and prevalent TB in HIV-infected adults enrolling at ZuziMpilo

The following patient characteristics were found to be significantly associated with Prevalent TB; sex, BMI, WHO Clinical Stage, CD4 count, duration on HAART, employment status, monthly income, financing of care and source of knowledge about ZuziMpilo. Table 3.2 outlines the results of contingency table using Pearson's χ^2 test,, the Fischer's exact test for categorical variables with any category containing less than five values and the Student's t-test for normally distributed continuous variables.

Table 3-3: Associations between patient characteristics and Prevalent TB

Characteristic	Prevalent TB (n=156)	No TB (n=1737)	P value$^{\Sigma}$
Age	**Median (IQR)**	**Median (IQR)**	
	31 (26 – 38)	32.5 (28 – 38)	0.357$^{\Psi}$
Age	**N (%)**	**N (%)**	
< 30 years	704 (93.00)	53 (7.00)	0.099
30 to 39.9 years	662 (90.07)	73 (9.93)	
≥ 40 years	371 (95.52)	30 (7.48)	
Sex			
Female, n (%)	82 (7.19)	1058 (92.81)	**0.041**
Male, n (%)	74 (9.83)	679 (90.17)	
Ethnicity			
Black	148 (8.52)	1589 (91.48)	0.234$^{\Omega}$
Coloured	1 (6.25)	15 (93.75)	
White	2 (16.67)	10 (83.33)	
Other	0 (0.00)	3 (100)	
Missing	5 (4.00)	120 (96.00)	
BMI			
Obese	5 (2.12)	231 (97.88)	**0.000**
Overweight	33 (7.22)	424 (92.78)	
Normal weight	81 (11.33)	634 (88.67)	
Underweight	36 (23.23)	119 (76.77)	
Missing	1 (99.7)	329 (99.70)	
WHO stage			
Stage 1	7 (2.43)	281 (97.57)	**0.000**
Stage 2	17 (4.53)	358 (95.47)	
Stage 3	61 (22.43)	211 (77.57)	
Stage 4	37 (27.41)	98 (72.59)	
Missing	34 (4.13)	789 (95.87)	
CD4 count			
>350	547 (98.92)	6 (1.08)	**0.000**
201 to 350	446 (96.33)	17 (3.67)	
<200	609 (82.97)	125 (17.03)	
Missing	135 (94.41)	8 (5.59)	
HAART status			
HAART naïve	136 (8.62)	1442 (91.38)	0.181

Characteristic	Prevalent TB (n=156)	No TB (n=1737)	P value[Σ]
Stared HAART	20 (6.35)	295 (93.65)	
Months on HAART			
HAART naive	136 (8.62)	1442 (91.38)	**0.011**
HAART < 6 months	11 (13.41)	71 (86.59)	
HAART > 6 months	9 (3.86)	224 (96.14)	
Smoking			
No smoking	129 (8.13)	1458 (91.87)	0.149
≤7 cigarettes/week	5 (4.39)	109 (95.61)	
>7 cigarettes/week	11 (12.94)	74 (87.06)	
Missing	11 (10.28)	96 (89.72)	
Alcohol use			
No alcohol	120 (8.75)	1251 (91.25)	0.295
<6 drinks/week	12 (5.06)	225 (94.94)	
≥6 drinks/week	11 (8.03)	126 (91.97)	
Missing	13 (8.78)	135 (91.22)	
Level of education			
Primary school	12 (7.89)	140 (92.11)	0.239
Secondary school	55 (10.24)	482 (89.76)	
Tertiary education	79 (7.27)	1007 (92.73)	
Missing	10 (8.47)	108 (91.53)	
Employment status			
Not unemployed[Π]	109 (7.69)	1309 (92.31)	**0.027**
Unemployed	44 (11.17)	350 (88.83)	
Missing	3 (3.70)	78 (96.30)	
Monthly income			
< R1,000	46 (11.25)	363 (88.75)	**0.050**
R1,000 to R4,999	51 (8.50)	549 (91.50)	
> R5,000	36 (6.59)	510 (93.41)	
Missing	23 (6.80)	315 (93.20)	
Cell phone expenditure			
R0 to R200	108 (9.00)	1092 (91.00)	0.271
>R200	22 (6.57)	313 (93.43)	
Missing	26 (7.26)	332 (	
Medical Insurance			
Has medical insurance	14 (8.05)	1268 (91.42)	0.614
No medical insurance	119 (8.58)	160 (91.95)	
Missing	23 (6.93)	309 (93.07)	
Financing of care			
Self-funded	100 (7.60)	1215 (92.400	**0.002**
Funded by other	30 (14.71)	174 (85.29)	
Missing	26 (6.95)	348 (93.05)	

Characteristic	Prevalent TB (n=156)	No TB (n=1737)	P value$^{\Sigma}$
Knowledge of service			
Workplace	5 (9.62)	47 (90.38)	**0.014**
Health facility	33 (7.27)	421 (92.73)	
Mass media	28 (5.88)	448 (94.12)	
Partner, family or friend	63 (11.56)	482 (88.44)	
Missing	27 (7.38)	339 (92.62)	

Σ All P values are for Pearson's χ^2 test for categorical variables except where indicated otherwise.
Ψ Student's t-test for a normally distributed continuous variable
Ω Fisher's exact test
Π Not unemployed = employed (full-time, part-time and self-employed), pensioners and students

Men were more likely to have prevalent TB than women (9.8% of men vs. 7.2% of women, p = 0.041). Patients with normal and underweight BMI were more likely to have TB at enrollment, 11.3% and 23.2% respectively, compared with patients with overweight and obese BMI, 7.2% and 2.1% respectively, (p = 0.000).

Although many patients did not have recorded assessments of WHO Clinical stage, patients with advanced WHO Staging were more likely to have TB at enrollment. Of those classified as WHO Stages 1 and 2, 2.4% and 4.5% respectively were diagnosed with prevalent TB in comparison with those classified as WHO Stages 3 and 4, of whom 22.4% and 27.4% respectively were diagnosed with prevalent TB (p = 0.000). Patients with a very low CD4 count were far more likely to have prevalent TB than those with higher CD4 counts. While 17.0% of patients with a CD4 count < 200 cells/mm^3 had prevalent TB, patients with higher CD4 counts at enrollment, 201 to 350 cells/mm^3 and > 350 cells/mm^3, had TB prevalence rates of 3.7% and 1.1% respectively. While there was no significant difference with respect to the rate of prevalent TB between those who were HAART naïve

and those already on HAART at enrollment (p = 0.181), there was a significant difference when the duration of HAART exposure was considered. Patients who had been on HAART for 6 months or less at enrollment were more likely (13.4%) to have prevalent TB than those who had been on HAART for more than 6 months (3.9%), (p = 0.011).

With respect to employment status, the group of patients without employment was significantly more likely (11.2%) to have prevalent TB than those who were employed or had an income in the form of a pension or support while studying (7.7%) (p = 0.027). Similarly, a higher proportion of patients with monthly incomes below R1, 000 (11.3%) had prevalent TB compared with those who reported a monthly income of R1, 000 to R4, 999 (8.5%) and more than R5, 000 (6.6%), (p = 0.050). Those patients who did not cover the cost of their care at ZuziMpilo themselves were twice as likely (14.7%) to have prevalent TB compared to those who did fund their own care (7.6%), (p = 0.002).

Patients who had heard about ZuziMpilo from a partner, family member or friend were more likely (11.6%) to have TB at enrollment than patients who had heard about ZuziMpilo from the workplace (9.6%), a health facility (7.3%) or from the mass media (5.9%) , (p = 0.014).

3.4. Determining risk factors for Prevalent TB in adult HIV-infected patients enrolling at ZuziMpilo

*3.4.1. **Univariate logistic regression***

Univariate logistic regression analysis (Table 3.3) confirmed most of the significant associations identified by contingency table analysis above (Table 3.2), elucidated the nature and magnitude of these potentially predictive relationships and informed the design of the final multivariate regression model. In the unadjusted analysis, as for contingency table analysis, significant risk factors for prevalent TB included sex, BMI, WHO Clinical Stage, CD4 count, months on HAART, employment status, monthly income and financing of care. However, in contrast to the contingency table analysis, age was identified as an additional predictor for prevalent TB using univariate logistic regression while source of knowledge about ZuziMpilo was not.

*3.4.2. **Significant risk factors***

While there was no significant relationship between age and the rate of prevalent TB using contingency table analysis, age was revealed to be a significant predictor of prevalent TB using univariate logistic regression. Patients in their thirties were 46% more likely than patients under 30 years of age to have prevalent TB (OR = 1.46, CI 1.01 – 2.12, p = 0.043). Males were more likely to have prevalent TB than females (OR = 1.41, CI 1.01 – 1.95, p = 0.042). Relative to obese patients, patients who were overweight (OR = 3.60 CI 1.38- 9.34, p = 0.009), normal weight (OR = 5.90, CI 2.36 – 14.75, p = 0.000), or

underweight (OR = 13.98, CI 5.35 – 36.55, p = 0.000) were increasingly more likely to have prevalent TB, suggesting a strong dose response relationship.

The risk of prevalent TB increased with advancing WHO Clinical Stage, relative to WHO Clinical Stage 1 or asymptomatic HIV disease. The lower the CD4 count at enrollment, the greater the risk of prevalent TB; patients with CD4 counts between 200 and 350 cells/mm^3 were more likely to have prevalent TB than those with CD4 counts above 350 cells/mm^3 (OR = 3.48, CI 1.36 – 8.89, p = 0.009). The risk was even greater for those with CD4 counts of 200 cells/mm^3 and below (OR = 18.71, CI 8.18 – 42.79, p = 0.000).

Patients who were unemployed were 51% more likely to be diagnosed with TB at enrollment than those who were not unemployed (OR = 1.51, CI 1.04 – 2.18, p = 0.029).

Patients who did not fund their care at ZuziMpilo themselves were twice as likely to have prevalent TB as those who financed their care themselves (OR = 2.09, CI 1.35 – 3.25, p = 0.001).

3.4.3. ***Significant protective factors***

Patients who had been on HAART for longer than 6 months were 57% less likely to have prevalent TB compared with patients who were HAART-naïve (OR = 0.43, CI 0.21 – 0.85, p = 0.015). Compared with patients who earned an income of less than R1, 000/month, those who earned a monthly income greater than R5, 000 were 44% less likely to have prevalent TB. (OR = 0.56, CI 0.35 – 0.88, p = 0.007).

3.4.4. ***Multivariate logistic regression***

The final multivariate logistic regression model (Table 3.3) included all variables with a p value < 0.2 and included the following variables: age, sex, BMI, CD4 count, smoking history, alcohol use history, employment status, monthly all-source income, monthly cell phone expenditure and source of funding for ZuziMpilo care. WHO Clinical Stage was excluded from the model because TB is one of the most common staging conditions for WHO Clinical Stages 3 and 4.

There was no collinearity between any of the variables (Appendix 6.2). The highest Spearman's correlation coefficients were between income and cell phone expenditure (ρ = 0.61) and medical insurance and cell phone expenditure (ρ = 0.62). The multivariable regression analysis was repeated restricting inclusion of variables to those with $p < 0.050$ on the univariate logistic regression. However, diagnostic tests evaluating the models for specification error, goodness of fit and the presence and influence of influential points favoured the initial model which included all variables with $p < 0.20$.

BMI, CD4 count and duration of exposure to HAART emerged as significant predictors of prevalent TB, adjusting for all other variables contained in the model (age, sex, smoking history, alcohol use history, employment status, monthly all-source income, monthly cell phone expenditure and source of funding for ZuziMpilo care). For BMI, adjusted ORs were of lesser magnitude but maintained the clear dose response relationship. Compared to obese patients, overweight patients were more than twice as likely (aOR = 2.83 CI 1.06 – 7.52, p

= 0.037), normal weight patients were 3.7 times more likely (aOR = 3.72, 1.44 – 9.60, p = 0.007) and underweight patients were more than six times more likely to have prevalent TB (aOR = 6.42, CI 2.33 – 17.70, p = 0.000). With respect to CD4 count, a CD4 count of < 200 cells/mm^3 predicted an 11.3 times increased risk of prevalent TB relative to CD4 count greater than 350 cells/mm^3 (aOR = 11.27, CI 4.84 – 26.28, p = 0.000). Patients exposed to HAART for longer than 6 months were significantly less likely to have prevalent TB than HAART-naïve patients (aOR = 0.47, CI 0.23 – 0.98, p = 0.043).

Table 3-4: Univariate and multivariate analysis of characteristics influencing prevalent TB using logistic regression.

Characteristic	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age				
< 30 years	Reference		Reference	
30 to 39.9 years	**1.46 (1.01 - 2.12)**	**0.043**	1.27 (0.84 - 1.92)	0.255
≥ 40 years	1.07 (0.67 - 1.71)	0.763	0.79 (0.48 - 1.31)	0.362
Sex				
Female, n (%)	Reference		Reference	
Male, n (%)	**1.41 (1.01 - 1.95)**	**0.042**	0.92 (0.62 - 1.39)	0.690
Ethnicity				
Black	Reference		Not included in model	
Coloured	2.14 (0.09 - 5.46)	0.747		
White	2.14 (0.46 - 9.89)	0.327		
Other	Omitted			
Missing	0.44 (0.18 - 1.11)	0.083		
BMI				
Obese	Reference		Reference	
Overweight	**3.60 (1.38 - 9.34)**	**0.009**	**2.83 (1.06 - 7.52)**	**0.037**
Normal weight	**5.90 (2.36 - 14.75)**	**0.000**	**3.72 (1.44 - 9.60)**	**0.007**
Underweight	**13.98 (5.35 - 36.55)**	**0.000**	**6.42 (2.33 - 17.70)**	**0.000**
Missing	0.14 (0.12 - 1.21)	0.074	0.13 (0.01 - 1.13)	0.064
WHO stage				
Stage 1	Reference		Not included in model	
Stage 2	1.91 (0.78 - 4.66)	0.157		

Characteristic	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Stage 3	**11.61 (5.20 - 25.89)**	**0.000**		
Stage 4	**15.16 (6.54 - 35.10)**	**0.000**		
Missing	1.73 (0.76 - 3.95)	0.193		
CD4 count	Reference			
>350	Reference		Reference	
201 to 350	**3.48 (1.35 - 8.89)**	**0.009**	**2.79 (1.09 - 7.22)**	**0.034**
<200	**18.71 (8.18 - 42.79)**	**0.000**	**11.27 (4.84 - 26.28)**	**0.000**
Missing	**5.40 (1.84 - 15.83)**	**0.002**	**5.81 (1.94 - 17.45)**	**0.002**
HAART status				
HAART naïve	Reference		Not included in model	
Stared HAART	0.72 (0.44 - 1.17)	0.183		
Months on HAART				
HAART naive	Reference		Reference	
HAART < 6 months	1.64 (0.85 - 3.18)	0.140	1.26 (0.62 - 2.57)	0.524
HAART > 6 months	**0.43 (0.21 - 0.85)**	**0.015**	**0.47 (0.23 - 0.98)**	**0.043**
Smoking				
No smoking	Reference		Reference	
≤7 cigarettes/week	0.52 (0.21 - 1.290	0.159	0.52 (0.19 - 1.41)	0.198
>7 cigarettes/week	1.68 (0.87 - 3.250	0.122	1.57 (0.72 - 3.42)	0.255
Missing	1.30 (0.68 - 2.48)	0.435	1.62 (0.52 - 5.02)	0.403
Alcohol use				
No alcohol	Reference		Reference	
<6 drinks/week	0.56 (0.30 - 1.02)	0.059	0.80 (0.41 - 1.55)	0.504
≥6 drinks/week	0.91 (0.48 - 1.73)	0.774	1.00 (0.46 - 2.180	0.995
Missing	1.00 (0.55 - 1.83)	0.990	1.12 0.36 - 3.49)	0.845
Level of education				
Primary school	Reference		Not included in model	
Secondary school	1.33 (0.69 - 2.560	0.390		
Tertiary education	0.92 (0.49 - 1.72)	0.784		
Missing	1.08 (0.45 - 2.59)	0.863		
Employment status				
Not unemployed[Π]	Reference		Reference	
Unemployed	**1.51 (1.04 - 2.18)**	**0.029**	0.79 (0.39 - 1.61)	0.514
Missing	0.46 (0.14 - 1.490	0.196	0.36 (0.10 - 1.32)	0.124
Monthly income				
< R1,000	Reference		Reference	
R1,000 to R4,999	0.73 (0.48 - 1.16)	0.147	0.58 (0.27 - 1.250	0.164
> R5,000	**0.56 (0.35 - 0.880**	**0.012**	0.63 (0.28 - 1.40)	0.254
Missing	**0.58 (0.34 - 0.97)**	**0.039**	0.71 (0.13 - 3.77)	0.685
Cell phone expenditure				
R0 to R200	Reference		Reference	

Characteristic	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
>R200	0.71 (0.44 - 1.14)	0.159	0.84 (0.50 - 1.43)	0.529
Missing	0.79 (0.51 - 1.24)	0.304	0.80 (0.27 - 2.39)	0.696
Medical Insurance				
Has medical insurance	Reference		Not included in model	
No medical insurance	0.93 (0.52 - 1.66)	0.812		
Missing	0.79 (0.50 - 1.26)	0.327		
Financing of care				
Self-funded	Reference		Reference	
Funded by other	**2.09 (1.35 - 3.25)**	**0.001**	1.14 (0.66 - 1.98)	0.633
Missing	0.91 (0.58 - 1.42)	0.672	0.79 (0.25 - 2.51)	0.687
Knowledge of service				
Workplace	Reference			
Health facility	0.74 (0.27 - 1.98)	0.544	Not included in model	
Mass media	0.59 (0.22 - 1.59)	0.296		
Partner, family or friend	1.23 (0.47 - 3.24)	0.674		
Missing	0.75 (0.27 - 2.040	0.571		

Π Not unemployed = employed (full-time, part-time and self-employed), pensioners and students

*3.4.5. **Sensitivity Analysis***

The analysis was repeated using a dataset that included the 39 patients classified as "Suspected TB" in the case definition for prevalent TB. The results are shown in Appendix 6.2. In this analysis, 195 patients have prevalent TB at enrolment, which translates into a prevalence rate of 10.30%. BMI, CD4 count, duration of exposure to HAART, current smoking history and the source of funding for ZuziMpilo care were found to be significant predictors of prevalent TB, adjusting for all the other variables contained in the model (age, sex, current alcohol use history, employment status, monthly all-source income, monthly cell phone expenditure and source of knowledge about ZuziMpilo).

4. DISCUSSION

This chapter discusses the major findings of the study and their meaning and importance in relation to the findings of other studies. It addresses the relevance and generalisability of the findings and closes with a reflection on the limitations of the study.

This study aimed to determine the prevalence of TB among HIV-positive patients enrolling at a fee-for-service, dedicated HIV clinic in downtown Johannesburg and to identify the factors that predict prevalent TB in this population. The findings were that 8.24% of adult ZuziMpilo clinic attendees who enrolled over a 29 month period between 1 August 2009 and 31 December 2011 had prevalent TB at enrollment and that significant predictors for prevalent TB included non-obese BMI, CD4 count <350 cells/mm^3 and duration on HAART of longer than six months.

4.1. TB prevalence

The TB prevalence at enrollment of 8.24% reported for this study approximates the prevalence of 8% reported in a study by Hanrahan et al for patients enrolling at an HIV Wellness clinic in Soweto in Gauteng province (40), but is markedly lower than TB prevalence reported for other dedicated HIV clinics, both within and outside Gauteng Province. For example, TB prevalence at enrolment was estimated at 42.5% (in 2007) and 34.7% (in 2007/8) in the Western Cape Province townships Kayelitsha and Gugulethu

respectively (39, 43), at 23% (in 2004 to 2007) in suburban Johannesburg, Gauteng province and at 20% (in 2007/8) in suburban Durban, KwaZulu-Natal province (33, 39). There are several potential explanations for these differences, including; varying regional TB rates (the prevalence of TB is relatively higher in Western Cape townships), varying regional HIV burdens, the varying thoroughness of TB screening and varying case definitions for prevalent TB (the case definitions for all the studies broader than the case definition used in this study). However, the most influential factor is likely to be the differing levels of immunosuppression at enrolment, reflected in the median CD4 count measurements. The two studies that report the lowest TB prevalence (approximately 8%) also report the highest median CD4 counts. Specifically, the median CD4 count for this study was 239 cells/mm^3 (IQR 110 – 405) while the median CD4 count for the study at a non-fee paying HIV Wellness clinic at a tertiary public sector hospital in Soweto was 285 cells/mm^3 (153 – 452). In comparison, the other four studies, conducted in Kayelitsha, Gugulethu, Johannesburg and Durban reported median CD4 counts that ranged from 42 to 131 cells/mm^3 and TB prevalence rates that ranged from 16% to 43%.

4.2. Predictors of TB

In terms of factors that predict prevalent TB, the results of this study are consistent with the findings of several other published studies.

4.2.1. ***CD4 count***

In this study, compared to CD4 counts greater than 350 cells/mm^3, CD4 counts of < 200 cells/mm^3 predicted an 11.3 fold increased risk of prevalent TB (aOR = 11.27, CI 4.84 – 26.28, p = 0.000) and CD4 counts ranging from 201 to 350 cells/mm^3 predicted an 2.8 fold increased risk of prevalent TB (aOR = 2.79, CI 1.09 – 7.22, p = 0.034). These results are consistent with well-established findings of numerous prior studies that have identified advanced immunodeficiency (low CD4 count) as one of the most important risk factors for TB (38, 39, 41, 54, 55).

4.2.2. ***Body Mass Index***

In this analysis, individuals who were not obese had greater risk of prevalent TB, the risk increasing in a dose response fashion as the BMI decreased. These findings are consistent with the findings of a number of studies that identify BMI as a strong, independent risk factor for mortality and tuberculosis among HIV infected adults (40, 62, 63, 66). One of these studies was designed to elucidate the relationship between BMI and all-cause mortality and incident TB among HIV infected adults. The study, conducted by Hanrahan et al showed a clear protective effect of increasing BMI on incident TB, also with a dose response, in 3635 HIV-infected adults attending a Soweto HIV wellness clinic.(40)

In the current study, the magnitudes of the ORs for overweight, normal weight and underweight BMIs yielded by multivariable analysis are markedly greater than those yielded by univariate analysis. For example, in the univariate analysis, an underweight person is almost 14 times more likely (OR = 13.98, CI 5.35 – 36.55) to have prevalent TB

than an obese person. In the multivariable analysis, however, the aOR drops to less than half this OR, i.e., an underweight person is just over 6 times more likely to have prevalent TB, taking into account all the variables included in the model.[1] Likely potential confounders in this model include sex, age and CD4 count. Controlling for confounding is especially critical when doing a cross-sectional evaluation of this nature because weight loss, and thus decreasing BMI, is a classic sign of both TB and advancing HIV disease. Thus the biological mechanism behind a single measure of low BMI is hard to evaluate (40). Without serial measurements it is difficult to assess whether the current BMI is lower than "normal" for a patient and if so, if it is a sign of TB and/or a sign of progressive HIV disease. On the other hand, it could be the current nutritional status of obese patients relative to those with lower BMIs that is driving the apparent protective effect. By including CD4 count in the multivariable model it was possible to tease out the contribution of underlying immunodeficiency and illness to the BMI and thus the contribution of obesity and higher BMIs to reduction of the risk of prevalent TB.

4.2.3. ***Duration of HAART***

This analysis confirms the effectiveness of long-term HAART in reducing the incidence of TB among HIV-positive individuals in sub-Saharan Africa (67-69). Although TB prevalence did not vary significantly between those on and off HAART, when it was

[1] age, sex, CD4 count, smoking history, alcohol use history, employment status, monthly all-source income, monthly cell phone expenditure and source of funding for ZuziMpilo care

analysed in terms of the duration of exposure to HAART, patients who had been on HAART for longer than 6 months at their first visit to ZuziMpilo were 53% less likely to have prevalent TB than HAART-naïve patients (aOR = 0.47, 95% CI 0.23 – 0.98, P = 0.043), after adjusting for age, sex, BMI, CD4 count, alcohol and tobacco consumption history, monthly all-source income, source of funding for ZuziMpilo care and source of knowledge about ZuziMpilo. This result is consistent with the well-established finding that TB incidence remains high in the first few months following HAART initiation – a combination of prevalent disease missed at baseline screening, including subclinical TB unmasked by the initial rapid restoration of the immune system (TB IRIS), and new infections (45, 67, 83). Over time HAART restores CD4 cell function and numbers and the risk of TB declines - although it never reaches the levels associated with HIV seronegative individuals. This association between CD4 count and duration of HAART is evident in this study; significantly fewer patients who had been on HAART for 6 months (26.2%) had profound immunosuppression (CD4 count < 200 cells/mm$^{3)}$, compared to those who had been on HAART for less than 6 months (46.3%), (P = 0.000).

4.2.4. ***Poor socio-economic status***

This study did not find an independent association between socioeconomic markers and prevalent TB. It is possible that socioeconomic status is not fully captured in the variables used in this study; monthly income, monthly cell phone expenditure and ability to fund own ZuziMpilo care. However, the more likely reason is that the population of patients who seek care at ZuziMpilo by definition fit into a higher socioeconomic bracket that is not

exposed to the socioeconomic factors that independently predispose to TB risk. Access to alternative economic resources that buffer them from these factors is implied by the fact that they attend a fee-paying service, even for those who are unemployed and/or unable to pay for their own ZuziMpilo care.

4.2.5. ***Smoking and alcohol consumption***

It is not surprising that there was no association, even in the unadjusted analysis, between current alcohol and tobacco use history and the risk of prevalent TB in this study given the poor quality of the data captured and the fact that there were very few patients who reported heavy exposure. The poor data quality of the data for these variables and the strong suggestion of reporter bias are discussed in detail under the section on limitations below.

4.3. Strengths and limitations

The strengths and limitations of this study are discussed with respect to the classification of the outcome and exposure variables, the management of confounding, and the relevance and generalisability of the results:

4.3.1. ***Classification of variables:***

The **case definition for prevalent TB** in this study was specific, including only cases with laboratory evidence for *M. tuberculosis*, or, failing this, evidence of clinical recovery (symptoms and signs) after commencement of TB treatment. Therefore, unlike several

other TB prevalence studies discussed in this report that used broader case definitions, it is unlikely that patients with TB at their first clinic visit were overstated, increasing the validity of the independent associations observed. It is possible, however that the estimate of TB prevalence underestimates the true prevalence, partly because sputum microscopy is less sensitive in HIV-infected patients (24, 25) and partly because clinical diagnoses of TB made at ZuziMpilo were frequently not followed by laboratory confirmation, though seeking laboratory confirmation is considered standard practice at the clinic. This introduces an element of measurement bias. Moreover, it is possible that the prevalence of TB at enrollment would increase if there had been appropriate source document information available, chiefly laboratory reports and clinical findings from follow up visits, for the 39 patients for whom there was insufficient evidence for a definitive classification according to the study case definition.

There are potential sources of error in data collection that may have led to misclassification of exposure variables and undermined the quality of some variables more than others. This study was an observational retrospective study using secondary data generated by an electronic patient management tool, TherapyEdge^{TM}, which was not designed as a research data capture tool. Despite the numerous built-in logical and range checks, missing values, implausible values and errors in units of measurement were present. This is compounded by the fact that data were entered once in real time by multiple users at any one visit and not subjected to quality audits. Data concerning alcohol and tobacco use were particularly affected. For example, in response to the question asked at enrollment, "How many cigarettes do you smoke per week?" data entries included responses as variable as:

“4/month”, “4 per w” or numbers without units of measurement. This lack of clarity makes it difficult to interpret the responses and undermines confidence in the accuracy of the data and hence the validity of the results observed. Confidence in the accuracy is further undermined by a strong suspicion of reporter bias, i.e., participants underreporting their smoking behaviour. This is suggested by the high number of patients reporting themselves to be non-smokers (83.8%) and the relatively modest number of cigarettes reportedly smoked per week (4.5% of participants reported smoking more than 7 cigarettes per week).

With regard to the analysis of missing values (Appendix 6.1), it makes sense that patients for whom a value for WHO Stage had been recorded had a significantly higher prevalence of TB than patients with missing values for WHO Stage ($P < 0.050$) because a diagnosis of pulmonary or extra pulmonary TB is a key and common staging condition for WHO Stages 3 and 4 respectively. This variable was excluded from the multivariable logistic regression. With BMI, patients for whom both height and weight were recorded had a significantly higher prevalence of TB than patients with missing values ($P < 0.050$), which may suggest that clinicians at ZuziMpilo were motivated to take or record anthropometric measurements for reasons related to the outcome variable, for example, because the patient already had a diagnosis of TB at enrollment or because the patient appeared to be unwell. Despite this significant association, the missing data did not bias results of the analysis because missing data were assigned a unique category in each variable.

*4.3.2. **Management of confounding***

Multivariable logistic regression was used to manage the potentially biasing effect of confounding variables. There remains the possibility that there are unmeasured confounders that exert bias on the findings. For example, data about haemoglobin levels were not collected and included in the analysis and it is possible that anaemia could be an unmeasured confounder in the relationship between BMI and the outcome of interest. However, the significance and magnitude of the independent associations observed in this study are coherent with published reports of analyses that have included anaemia as a variable and it is unlikely that possible residual confounding in this study would change these findings substantially.

*4.3.3. **Relevance and generalisability of the results***

This study has describes a unique population with the capacity to pay a subsidised monthly fee for their HIV care. Thus, the study sample may not be generalisable to the large population of HIV-infected adults in South Africa, who receive free health care in public sector facilities. This is certainly true of the lack of an independent association observed between different levels of socio economic markers and the prevalence of TB at enrollment. These findings may certainly be more generalisable to other clinics that provide services for a subsidized monthly fee and this information may be especially important if this model is replicated and scaled up in private and semi-private facilities around the country.

However, this study has great clinical relevance because it corroborates the growing body of evidence that underpins several key recommendations that have the potential to reduce

mortality from TB in those people infected with HIV; vigilant and regular routine TB screening in HIV-infected patients at all CD4 counts and especially in those with profound immunosuppression and in the first three to four months following HAART initiation, the urgent development and distribution of more sensitive and point of care diagnostic tests for TB in HIV-infected patients at all levels of health care (most especially primary health care facilities) and the importance of initiation of HAART in individuals with active tuberculosis regardless of WHO clinical stage or CD4 count This study also highlights the importance of regular, routine anthropometric measurement, even in relatively affluent populations.

5. CONCLUSION

This study found that approximately 8 out of every 100 HIV-infected adults enrolling at a fee-for-service dedicated HIV clinic in downtown Johannesburg had prevalent TB disease. This was a relatively healthy population, as indicated by the median CD4 count, and this prevalence approximates to that estimated in a non-fee-paying clinic population in Soweto, Gauteng with similar levels of immunosuppression. Profound immunosuppression, non-obese and decreasing BMI and less than 6 months exposure to HAART were confirmed as powerful predictors of TB risk among HIV-infected individuals in a relatively affluent setting. This study highlights that BMI is a useful proxy marker of TB risk among HIV-positive individuals. Height and weight are easily assessed anthropomorphic measures and should be conducted routinely in all patients at regular intervals.

6. APPENDIX

6.1. Analysis of missing values

The Chi-squared test was used to investigate whether missing data in each variable were associated with the outcome (Prevalent TB) in order to assess potential sources of bias and how these could be dealt with. Missing data for the variables WHO Clinical Stage and BMI were associated with Prevalent TB. The potential influence of these associations and measures taken to minimize bias are covered in the discussion.

Table 6-1: Analysis of the association between missing values for each variable and Prevalent TB using the Chi-squared test

Characteristic	No TB		Prevalent TB		P value
	N	%	N	%	
Ethnicity					
Non-missing	1617	91.46	151	8.54	0.090
Missing	120	96.00	5	4.00	
BMI					
Non-missing	1408	90.08	155	9.92	**0.000**
Missing	329	99.70	1	0.30	
WHO stage					
Non-missing	948	88.60	122	11.40	**0.000**
Missing	789	95.87	34	4.13	
CD4 count					
Non-missing	1602	91.54	148	8.46	0.231
Missing	135	94.41	8	5.59	
Smoking					
Non-missing	1602	91.81	143	8.19	0.403
Missing	135	91.22	13	8.78	
Alcohol use					
Non-missing	1641	91.88	145	8.12	0.802
Missing	96	89.72	11	10.28	

Characteristic	No TB		Prevalent TB		P value
	N	%	N	%	
Level of education					
Non-missing	1629	91.77	146	8.23	0.924
Missing	108	91.53	10	8.47	
Employment status					
Non-missing	1659	91.56	153	8.44	0.129
Missing	78	96.30	3	3.70	
Monthly income					
Non-missing	1422	91.45	133	8.55	0.289
Missing	315	93.20	23	6.80	
Monthly cell phone expenditure					
Non-missing	1405	91.53	130	8.47	0.455
Missing	332	92.74	26	7.26	
Medical Insurance					
Non-missing	1428	91.48	133	8.52	0.338
Missing	309	93.07	23	6.93	
Financing of care					
Non-missing	1389	91.44	130	8.56	0.312
Missing	348	93.05	26	6.95	
Knowledge of service					
Non-missing	1398	91.55	129	8.45	0.503
Missing	339	92.62	156	7.38	

6.2. Sensitivity Analysis:

Analysis with alternative dataset that includes the 39 patients classified as "Suspected TB" in the study case definition: 195 patients with prevalent TB

Table 6-2: Associations between patient characteristics and Prevalent TB

Characteristic	Prevalent TB (n=195)	No TB (n=1698)	P value$^{\Sigma}$
Age	**Median (IQR)**	**Median (IQR)**	
	33 (28 – 39)	31 (26 – 38)	0.030 $^{\Psi}$
Age	**N (%)**	**N (%)**	
< 30 years	62 (8.19)	695 (91.81)	0.035
30 to 39.9 years	90 (12.24)	645 (87.76)	
≥ 40 years	43 (10.72)	358 (89.28)	
Sex			
Female, n (%)	97 (8.51)	1043 (91.49)	0.002
Male, n (%)	98 (13.01)	655 (86.99)	
Ethnicity			
Black	184 (10.59)	1553 (89.41)	0.268$^{\Omega}$
Coloured	2 (12.50)	14 (87.50)	
White	2 (16.67)	10 (83.33)	
Other	0 (0.00)	3 (100.00)	
Missing	7 (5.60)	118 (94.40)	
BMI			
Obese	6 (2.54)	230 (97.46)	0.000
Overweight	41 (8.97)	416 (91.03)	
Normal weight	102 (14.27)	613 (85.73)	
Underweight	42 (27.10)	113 (72.90)	
Missing	4 (1.21)	326 (98.79)	
WHO stage			
Stage 1	7 (2.43)	281 (97.57)	0.000
Stage 2	22 (5.87)	353 (94.13)	
Stage 3	80 (29.41)	192 (70.59)	
Stage 4	48 (35.56)	87 (64.44)	
Missing	38 (4.62)	785 (95.38)	
CD4 count			
>350	9 (1.63)	544 (98.37)	0.000
201 to 350	20 (4.32)	443 (95.68)	
<200	154 (20.98)	580 (79.02)	
Missing	12 (8.39)	131 (91.61)	

Characteristic	Prevalent TB (n=195)	No TB (n=1698)	P value[Σ]
HAART status			
HAART naïve	170 (10.77)	1408 (89.23)	0.130
Stared HAART	25 (7.94)	290 (92.06)	
Months on HAART			
HAART naive	170 (10.77)	1408 (89.23)	**0.002**
HAART < 6 months	14 (17.070	68 (82.93)	
HAART > 6 months	11 (4.72)	222 (95.28)	
Smoking			
No smoking	162 (10.21)	1425 (89.79)	0.096
≤7 cigarettes/week	6 (5.26)	108 (94.74)	
>7 cigarettes/week	13 15.290	72 (84.710	
Missing	14 (13.08)	93 (86.92)	
Alcohol use			
No alcohol	144 (10.50)	1227 (89.50)	0.394
<6 drinks/week	18 (7.59)	219 (92.41)	
≥6 drinks/week	15 (10.95)	122 (89.05)	
Missing	18 (12.16)	130 (87.84)	
Level of education			
Primary school	18 (11.84)	134 (88.16)	0.211
Secondary school	65 (12.10)	472 (87.90)	
Tertiary education	98 (9.02)	988 (90.98)	
Missing	14 (11.82)	104 (88.14)	
Employment status			
Not unemployed[Π]	133 (9.38)	1285 (90.62)	**0.006**
Unemployed	57 (14.47)	337 (85.53)	
Missing	5 (6.17)	76 (93.83)	
Monthly income			
< R1,000	59 (14.43)	350 (85.570	**0.020**
R1,000 to R4,999	58 (9.67)	542 (90.33)	
> R5,000	48 (8.79)	498 (91.21)	
Missing	30 (8.88)	308 (91.12)	
Cell phone expenditure			
R0 to R200	136 (11.33)	1064 (88.67)	0.103
>R200	25 (7.460	310 (92.54)	
Missing	34 (9.50)	324 (90.50)	
Medical Insurance			
Has medical insurance	148 (10.67)	1239 (89.33)	0.581
No medical insurance	18 (10.34)	156 (89.66)	
Missing	29 (8.73)	303 (91.27)	
Financing of care			
Self-funded	119 (9.05)	1196 (90.95)	**0.000**

Characteristic	Prevalent TB (n=195)	No TB (n=1698)	P value$^{\Sigma}$
Funded by other	43 (21.08)	161 (78.92)	
Missing	33 (8.82)	341 (91.18)	
Knowledge of service			
Workplace	8 (15.38)	44 (84.62)	**0.000**
Health facility	39 (8.59)	415 (91.41)	
Mass media	33 (6.93)	443 (93.07)	
Partner, family or friend	81 (14.86)	464 (85.14)	
Missing	34 (9.29)	332 (90.71)	

Σ All P values are for Pearson's χ^2 test for categorical variables except where indicated otherwise.
Ψ Student's t-test for a normally distributed continuous variable
Ω Fisher's exact test
Π Not unemployed = employed (full-time, part-time and self-employed), pensioners and students

Table 6-3: Univariate and multivariate analysis of characteristics influencing prevalent TB using logistic regression.

Characteristic	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age				
< 30 years	Reference		Reference	
30 to 39.9 years	1.56 (1.11 – 2.20)	0.010	1.36 (0.93 – 2.00)	0.116
≥ 40 years	1.35 (0.89 – 2.02)	0.154	0.98 (0.62 – 1.55)	0.930
Sex				
Female, n (%)	Reference		Reference	
Male, n (%)	1.61 (1.19 – 2.17)	0.002	1.07 (0.74 – 1.55)	0.707
Ethnicity				
Black	Reference		Not included in model	
Coloured	1.20 (0.27 – 5.35)	0.806		
White	1.69 (0.37 – 7.76)	0.501		
Other	omitted			
Missing	0.50 (0.23 – 1.10)	0.081		
BMI				
Obese	Reference		Reference	
Overweight	3.78 (1.58 - 9.03)	0.003	3.00 (1.22 – 7.41)	0.017
Normal weight	6.38 (2.76 – 14.73)	0.000	4.10 (1.71 – 9.84)	0.002
Underweight	14.25 (5.88 – 34.51)	0.000	6.07 (2.36 – 15.56)	0.000
Missing	0.47 (0.13 – 1.67)	0.247	0.42 (0.11 – 1.56)	0.195
WHO stage				
Stage 1	Reference		Not included in model	
Stage 2	2.50 (1.05 – 5.94)	0.038		
Stage 3	16.73 (7.56 – 37.00)	0.000		
Stage 4	22.15 (9.67 – 50.72)	0.000		
Missing	1.94 (0.86 – 4.400	0.111		
CD4 count	Reference			
>350	Reference		Reference	
201 to 350	2.73 (1.23 – 6.05)	0.014	2.05 (0.91 – 4.61)	0.083
<200	16.05 (8.11 – 31.75)	0.000	9.03 (4.47 – 18.22)	0.000
Missing	5.54 (2.29 – 13.42)	0.000	5.35 (2.14 – 13.38)	0.000
HAART status				
HAART naïve	Reference		Not included in model	
Stared HAART	0.71 (0.46 – 1.12)	0.132		
Months on HAART				
HAART naive	Reference		Reference	
HAART < 6 months	1.71 (0.94 – 3.10)	0.080	1.21 (0.62 – 2.36)	0.569
HAART > 6 months	0.41 (0.22 – 0.77)	0.005	0.46 (0.24 – 0.90)	0.023
Smoking				

Characteristic	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
No smoking	Reference		Reference	
≤7 cigarettes/week	0.49 (0.21 – 1.13)	0.094	0.38 (0.15 – 0.97)	0.042
>7 cigarettes/week	1.59 (0.86 – 2.93)	0.139	1.25 (0.60 – 2.61)	0.548
Missing	1.32 (0.74 – 2.38)	0.346	1.25 (0.47 – 3.38)	0.655
Alcohol use				
No alcohol	Reference		Reference	
<6 drinks/week	0.70 (0.42 – 1.18)	0.172	1.03 (0.58 – 1.83)	0.930
≥6 drinks/week	1.05 (0.60 – 1.84)	0.871	1.18 (0.58 – 2.39)	0.644
Missing	1.18 (0.70 – 1.99)	0.535	1.58 (0.58 – 4.26)	0.369
Level of education				
Primary school	Reference		Not included in model	
Secondary school	1.03 (0.59 – 1.79)	0.930		
Tertiary education	0.74 (0.43 – 1.26)	0.266		
Missing	1.00 (0.48 – 2.11)	0.996		
Employment status				
Not unemployed[Π]	Reference		Reference	
Unemployed	1.63 (1.17 – 2.28)	0.004	0.80 (0.42 – 1.55)	0.517
Missing	0.64 (0.25 – 1.60)	0.336	0.52 (0.18 – 1.50)	0.228
Monthly income				
< R1,000	Reference		Reference	
R1,000 to R4,999	0.63 (0.43 – 0.93)	0.021	0.64 (0.31 – 1.31)	0.222
> R5,000	0.57 (0.38 – 0.86)	0.007	0.85 (0.40 – 1.80)	0.673
Missing	0.58 (0.36 – 0.92)	0.021	0.54 (0.10 – 3.02)	0.483
Cell phone expenditure				
R0 to R200	Reference		Reference	
>R200	0.63 (0.40 – 0.98)	0.042	0.76 (0.46 – 1.25)	0.280
Missing	0.82 (0.55 – 1.22)	0.329	0.99 (0.36 – 2.71)	0.982
Medical Insurance				
Has medical insurance	Reference		Not included in model	
No medical insurance	0.97 (0.58 – 1.62)	0.895		
Missing	0.80 (0.53 – 1.22)	0.298		
Financing of care				
Self-funded	Reference		Reference	
Funded by other	2.68 (1.83 – 3.95)	0.00	1.71 (1.03 – 2.84)	0.039
Missing	0.97 (0.65 – 1.46)	0.893	0.72 (0.23 – 2.25)	0.574
Knowledge of service				
Workplace	Reference		Reference	
Health facility	0.52 (0.23 – 1.18)	0.115	0.74 (0.30 – 1.83)	0.513
Mass media	0.41 (0.18 – 0.94)	0.036	0.73 (0.29 – 1.85)	0.512
Partner, family or friend	0.96 (0.44 – 2.11)	0.920	1.21 (0.50 – 2.95)	0.670
Missing	0.56 (0.25 – 1.29)	0.176	1.21 (0.32 – 4.49)	0.778

6.3. Assessment of collinearity between exposure variables using the Spearman's correlation test

	Sex	Age	CD4 count	WHO Stage	BMI	Level of education
Sex	1					
Age	0.1749	1				
CD4 count	0.1192	0.0648	1			
WHO Stage	-0.009	-0.0429	-0.1052	1		
BMI	0.134	-0.0831	0.0752	0.3161	1	
Level of education	-0.0463	-0.1857	-0.0541	0.0521	-0.0121	1
Employment status	0.0818	0.0224	-0.0381	0.0378	-0.0464	0.127
Monthly income	0.106	-0.0025	0.0007	0.0461	-0.0243	0.1211
Monthly cell phone expenditure	0.0764	-0.0351	0.0322	0.0094	-0.0139	0.0366
Knowledge of service	0.0307	0.002	0.0631	0.0676	0.0912	-0.0267
Financing of care	-0.0059	0.0135	0.0974	-0.0023	0.0521	-0.123
Medical Insurance	0.0033	-0.0281	0.0208	0.0585	0.0275	0.0382

	Employment status	Monthly income	Cell phone expenditure	Knowledge of service	Financing of care	Medical Insurance
Sex						
Age						
CD4 count						
WHO Stage						
BMI						
Level of education						
Employment status	1					
Monthly income	0.5533	1				
Monthly cell phone expenditure	0.2304	0.6075	1			
Knowledge of service	0.0708	0.4033	0.4797	1		
Financing of care	-0.0088	0.3877	0.5429	0.5137	1	
Medical Insurance	0.2345	0.6842	0.6296	0.5524	0.6239	1

6.4. Human Research Ethics Committee (Medical) Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Lucy Connell

CLEARANCE CERTIFICATE	**M10M101177**
PROJECT	Risk Factors for Prevalent Tuberculosis in HIV-Infected Patients Attending a Free-Service HIV
Clinic	in Inner City Johannesburg
INVESTIGATORS	Dr Lucy Connell.
DEPARTMENT	School of Public Health
DATE CONSIDERED	26/11/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 26/11/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr N Martinson

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

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