Drug Resistant Tuberculosis Treatment Outcomes at an Urban Ambulatory TB Unit in the City of Johannesburg

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A dissertation submitted in partial fulfilment of Master of Science in the field of Infectious Disease Epidemiology.

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CANDIDATE DECLARATION:

I, Norah Maitisa declare that this research report is my own work, compiled under the supervision of Prof. Charles Chasela and Dr. Andrew Black. The report is being submitted to the University of the Witwatersrand in partial fulfilment of a degree of Master of Science in the field of Infectious Disease Epidemiology. There are no prior submissions of this material to other institutions for academic purposes.

Signature:

Dr Norah Maitisa

Date: 8 June 2018

DEDICATION:

I dedicate this report to my family, my loving husband Kgabo Maitisa, who encouraged and supported me throughout my studies and to my twin boys Mosa and Mogau Maitisa, may this inspire you to achieve greater heights.

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ABSTRACT:

Background: Treatment of Drug Resistant Tuberculosis has historically been centralised and this model of care has posed challenges in management of such patients. Prolonged time to treatment and potential risk for continued community and nosocomial transmissions, capacity at these sites and availability of human resources to treat the increasing numbers of DRTB patients has been among those challenges. WHO set out to improve all DRTB outcomes especially in countries where the burden is high. Decentralisation of DRTB care has shown to improve these outcomes in many settings.

Objectives: The main aim of the study was to describe any Rifampicin-resistant TB treatment outcomes in an ambulatory care model and to assess predictors of unsuccessful outcomes. Survival times for unsuccessful treatment outcomes were also determined. A comparison of the treatment outcomes by HIV status was also assessed.

Methods: A retrospective cohort review of 335 patients with any Rifampicin-resistant TB diagnosis between January 2010 and January 2014, at Charlotte Maxeke Johannesburg Academic hospital DR-TB focal point was conducted. Survival analysis was done for unsuccessful outcomes. Multivariable Cox regression models were used to determine predictors of mortality, default and overall unsuccessful outcomes. Differences in outcomes by HIV status were compared using Pearson's chi-square

Results: Of the 335 patients analysed, 14 (4.2%) patients were still on treatment, 64 (19.1%) were successfully treated [with 17 (5.1%) cured and 47 (14%) completed treatment]. Unsuccessful outcomes were seen in 122 (36.4%) of the patients [with 30 (9%) died and 92 (27.5%) defaulted]. The remaining 135 (40.3%) patients were transferred out. There were no treatment failures in this cohort. Median survival time for unsuccessful outcomes was 3.2 months (IQR:1.4 to 9.2). Median time to death and default were 4.6 months (IQR:0.9 to13.8) and 3 months (IQR:1.4 to 8.5) respectively. There was no statistical difference found in proportions of successful and unsuccessful outcomes between HIV co-infected and HIV negative patients. Overall predictors of unsuccessful outcomes were: confirmed RMR-TB (HR=8.5; 95% CI: 2.0-35.2; p=0.003) and unconfirmed Rifampicin-resistance diagnosed on GXP alone (HR=10.9; 95% CI: 2.6-44.8; p=0.001). There were no statistically significant predictors of mortality found in this study. Predictors of default were: confirmed RMR-TB (HR=15.9; 95% CI: 2.1-116.5; p=0.006) and unconfirmed Rifampicin-resistance diagnosed on

GXP alone (HR=17.2; 95% CI: 2.4-125.3; p=0.01). For a subgroup of HIV co-infected patients, being initiated on ART had 90% less hazards of defaulting (HR=0.1; 95% CI: 0.05-0.2; p=0.000). Age category >40 years also had 60% less hazards of defaulting in the HIV co-infected patients. Patients co-infected with HIV had higher hazards of default if they were diagnosed as confirmed RMR-TB (HR=10.8; 95% CI: 1.4-84.1; p=0.023) and unconfirmed Rifampicin-resistance diagnosed on GXP alone (HR=10.6; 95% CI: 1.4-80.2; p=0.022). Not initiated on ART was a predictor of unsuccessful outcome among HIV co-infected patients (HR=7.6; 95% CI: 4.1-14.1; p=0.000).

Conclusion: Overall treatment outcomes were poor, with a low success rate (19.1%) and a high defaulter rate (27.5%). Mortality was comparable with other studies. Predictors of unsuccessful outcomes were confirmed RMR-TB and Rifampicin-resistance diagnosis on GXP only. Being initiated on ART and age >40 years reduced odds of defaulting by 90% and 60% respectively among HIV co-infected patients.

Key recommendations: The high defaulter rate within the first few months of treatment impacts negatively on the control of DRTB, hence efforts to improve this are needed. Addressing factors associated with defaulting is crucial in DRTB clinics to curb transmission of DRTB in the community. All patients diagnosed with a GXP need immediate confirmation by LPA and culture/DST.

Key words: *Rifampicin resistant TB, Drug Resistant TB Treatment outcomes, Ambulatory DRTB care, DRTB/HIV co-infection*

ABBREVIATIONS

AIDS - Acquired Immunodeficiency Syndrome

AM - Amikacin

ART - Antiretroviral Therapy

ARVs - Antiretroviral Drugs

BMI - Body Mass Index

CD4 - Cluster of Differentiation 4

CI-95% - Confidence Interval at 95%

CP - Continuation Phase

DM - Diabetes Mellitus

DOTs - Directly Observed Therapy-Short Course Strategy

DR-TB - Drug Resistant Tuberculosis

DST - Drug Susceptibility Testing

ELISA - Enzyme-linked Immunosorbent Assay

EMB - Ethambutol

EPTB - Extra-pulmonary Tuberculosis

ETO - Ethionamide

HIV - Human Immunodeficiency Virus

IP - Intensive Phase

IQR - Interquartile Range

IRIS - Immune Reconstitution Inflammatory Syndrome

KM - Kanamycin

LPA - Line Probe Assay

MDR-TB - Multidrug Resistant Tuberculosis

MFX - Moxifloxacin

MGIT - Mycobacterial Growth Indicator Tube

MTB - Mycobacterial Tuberculosis

MOTT – Mycobacterium Other Than Tuberculosis

NHLS - National Health Service Laboratory

NICD – National Institute of Communicable Diseases

PTB - Pulmonary Tuberculosis

PZA - Pyrazinamide

RRTB – Rifampicin Resistant Tuberculosis

SD - Standard Deviation

SA - South Africa

ST - Still on Treatment

TB - Tuberculosis

TC - Treatment Completed

TD - Treatment Defaulted

TF - Treatment Failure

TO - Transfer Out

WHO - World Health Organization

XDRTB – Extensively Drug Resistant Tuberculosis

APPENDICES

Appendix 1: Plagiarism declaration form

Appendix 2: Bivariate Cox regression analysis for predictors of unsuccessful Outcomes (deaths and defaults)

Appendix 3: Test for proportional assumption

Appendix 4: Goodness of fit of final model

Appendix 5: Permission to use data from Charlotte Maxeke Johannesburg Academic Hospital

Appendix 6: Ethics clearance certificate from the University of Witwatersrand Research Ethics Committee

LIST OF FIGURES:

LIST OF TABLES

TABLE OF CONTENTS

1. CHAPTER 1: INTRODUCTION

This chapter gives an overview of the burden of tuberculosis (TB) and drug-resistant TB (DR-TB) in particular. It also outlines the rationale for the study and explores the literature of relevance to this study.

1.1 Background

There was an increasing trend in the number of reported cases of Drug Resistant (DR) Tuberculosis (TB) over the past few years. [1] The use of Gene XPert® MTB/RIF (GXP) approved for use by the World Health Organisation (WHO) has increased identification of DR-TB cases. [2] In South Africa (SA), the management of DR-TB has historically been centralised and institutionalised, where the patients were treated only within these central TB facilities. The centralised TB care model proved to have several challenges, including delayed time to DR-TB treatment initiation leading to decreased coverage of treatment. This meant that transmission in the community continued due to the delay but also that nosocomial transmissions increased for those who were hospitalized.[2, 7] The SA government, due to these challenges, have since proposed decentralisation and deinstitutionalisation of DR-TB patients.[2] These efforts were to decrease the delay in starting treatment, to increase treatment coverage and reduce DR-TB transmissions.[1] Decentralised or community care models in South Africa and elsewhere have been shown to be feasible and reduced delays in treatment initiation and improved survival of DRTB patients. [2, 3, 22, 26, 30]

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is one of the three central academic hospitals in the City of Johannesburg. Its outpatient DR-TB clinic is an urban decentralised site for the management of DR-TB in the City of Johannesburg, serving a very dense population with a high burden of TB and Human Immunodeficiency Virus (HIV) co-infection. Patients were referred from the feeder hospitals and primary health care centres and from within the hospital wards and outpatient departments with DR-TB diagnosis. These patients were only referred for admission at the centralised TB hospital, Sizwe Tropical and Infectious Disease Hospital (STIDH) when diagnosed with XDRTB or whenever an admission was warranted. Patients referred with Rifampicin resistant Xpert® MTB/RIF results were started on MDRTB treatment immediately while waiting for confirmation with Line Probe Assay (LPA), culture and Drug Sensitivity Testing (DST) results. The outpatient clinic offered integrated TB, HIV and chronic management services, a model which has shown better

treatment outcomes. [8, 9, 13] All patients with unknown HIV status and negative status were offered counselling and voluntary HIV testing. Antiretroviral therapy (ART) was also offered within this outpatient clinic. MDRTB was defined as Mycobacterium TB resistance to Isoniazid (INH) and Rifampicin (R), according to WHO definition.[60] Extensively drug resistant TB (XDRTB) was defined as the presence of MDR-TB plus resistance to any of the fluoroquinolones and any one of the second-line anti-tuberculous injectable drugs Amikacin (AM), Kanamycin (KM) and Capreomycin (CM).[60] In the clinic treatment for MDRTB was administered for 18 to 24 months, with a minimum of 5 drugs including an injectable drug during the first six months of intensive phase of treatment (Kanamycin, Moxifloxacin (MFX), Ethionamide (ETO), Terizidone (TDR), Ethambutol (EMB) and Pyrazinamide (PZA)). The intensive phase was followed by 12 months of four drugs MFX/ETO/PZA/TDR after culture conversion during the continuation phase.[59] Patients were started on treatment when they presented to the focal point clinic with a GXP result showing Rifampicin resistance. Their injectable drugs during intensive phase were administered daily by a nurse at primary health care centres closer to where they resided. Patients were followed up at 2 weeks, 4 weeks then every 4 weeks thereafter, to monitor clinical response, and blood tests, sputum culture/DST, side effects were also assessed at these visits.

In its National Strategic Plan, SA planned to improve the DRTB treatment success rate to 75%.[10] DRTB treatment outcomes can be improved if more resources and healthcare commitment is dedicated to the control of the disease.

1.2 Problem statement:

The DRTB clinic at CMJAH treated patients with DRTB not warranting an admission to the centralized unit. This population had a very high TB/HIV co-infection rate, highly mobile population treated in an ambulatory urban setting. HIV/TB coinfected patients with concomitant use of anti-TB drugs and ART were more likely to have adverse events and the worst treatment outcomes compared to HIV uninfected patients. [4, 33, 44] The World Health Organization (WHO) has reported poor DRTB treatment outcome globally in their 2017 report, with SA having success rates of 54% and 27% for MDR/RR-TB and XDRTB respectively. [33] Poor drug resistant TB treatment outcomes pose a major threat to the TB programme in the country. This has been a major public health concern as transmission of the resistant strains in the community occur if TB is not diagnosed and treated early and appropriately. The country aimed to improve their DRTB success rate to 75%, as stipulated in their National Strategic Plan. [10] Centralisation of care and institutionalisation of DRTB patients has been historically

been practiced in SA. Delays in initiating DR-TB treatment after diagnosis were still experienced due to the centralisation of DR-TB treatment and care and hence a move to decentralize DRTB care in SA.[12] The centralised TB hospital (STIDH) focus on treating DRTB cases in hospital, and the patients are referred from all over the Gauteng province for their treatment and management. This may increase the time it takes from the initial Rifampicin resistance diagnosis by Xpert® MTB/RIF to referral to the centre and to initiating anti-TB drugs, even when such testing has shown to decrease the time to treatment in TB patients. [16] Availability of beds to admit these patients at central DRTB hospitals has been a challenge in view of increased demand for hospitalisation for very sick patients with DRTB in SA. The decentralised and ambulatory care models treat all other mono-resistant, stable smear negative MDR-TB cases. Decentralisation and de-institutionalisation of treatment and care of DR-TB has shown to improve the time to TB treatment. [16] Understanding the predictors of poor DR-TB outcomes will facilitate the actions needed to be undertaken to improve these poor outcomes. [10, 33]

SA has a very high HIV prevalence, with 7.1 million people living with HIV which may have fuelled the TB burden.[63] Deaths due to TB in HIV co-infected patients were high in this region prior to Anti-Retroviral Therapy (ART) roll-out in SA compared to elsewhere, and they remained high even after the massive ART roll-out.[5, 14] ART coverage in TB/HIV co-infected patients has improved drastically and despite 88% of HIV/TB co-infected patients receiving ART, DRTB treatment outcomes remained poor despite the evidence that ART improve TB treatment outcomes with up to 86% reduction in mortality.[8, 13, 33]

1.3 Justification of the study

In SA DR-TB treatment outcomes have been evaluated for decentralised community DR-TB treatment and care models in rural and peri-urban communities. In these studies, patients were followed up in their communities by community nurses and/or counsellors. Treatment outcomes are needed in such a setting in an urban decentralised ambulatory clinic, with clinic-based outpatient care with a highly mobile population, without the healthcare workers going into the community for the patient's care and treatment. There is paucity of data reporting on any RR-TB outcomes in ambulatory decentralised settings other than treatment outcomes for MDR and XDR-TB in urban or peri-urban settings. This study evaluated outcomes of any Rifampicin resistant TB in an urban decentralized ambulatory care setting. SA's target is to increase the DR-TB treatment success rate to 75% according to the National Strategic Plan

(NSP). [10] DR-TB treatment outcomes in such a setting will inform whether ambulatory care model improve outcomes in a very mobile population and understanding the predictors of these outcomes is needed to improve DR-TB treatment outcomes and further curb the spread of DRTB in the community.

1.4 Research question:

What were the DR-TB treatment outcomes in a decentralized ambulatory urban setting and the predictors of unsuccessful outcomes?

1.5 Literature Review

1.5.1. Burden of DRTB

WHO estimated that 490 000 new cases of MDR-TB emerged globally in its 2017 TB Report. [33] This meant the incidence of DR/RRTB was 4.1%, with a higher incidence of 19% among patients previously treated for TB. WHO has defined 30 countries as having the highest burden and contributing hugely to the global burden of TB, and SA was among those high burden countries. [33] Locally in SA it was estimated that there were 19 000 incident cases of MDR/RR-TB in 2017according to the same report. [33]

A recent survey reported in 2017, investigating the burden of DRTB in SA between 2012 and 2014 from the National Institute for Communicable Diseases (NICD), reported a 3% MDRTB burden and an even higher Rifampicin mono-resistance burden of 5%, with a higher burden seen among those previously treated for TB. [48] The results are aligned with those reported by the WHO in their 2017 TB report which estimated TB cases with MDR/RR-TB was 4% in SA. [33] A cross-sectional survey by Cox et al, also showed a very high burden of MDRTB in an urban township in South Africa. [31] Similar burden of disease has been seen in other different studies done in DR-TB patients in SA. [5, 26, 31].

SA experienced the largest increase in the number of MDRTB between 2011 and 2012 as stated by a report by WHO from a Think Tank Meeting held in SA [12], although a decline has been achieved during the 2017 reporting year according to WHO. [33] The high prevalence of HIV has fuelled the incidence of TB in this region. SA has one of the highest TB and HIV co-infection rates. [48] Wells et al has referred to this high HIV burden causing a rise in TB incidence the “perfect storm”. [61] In the recent TB survey in SA, the rate of TB and HIV co-infection was higher within the Gauteng province at 75%. [48] There was a high rate of DR-TB among patients staring ART in SA. [27] HIV itself has been associated with development of

Rifampicin mono-resistance in a case control study. [18] TB was among the top conditions causing death worldwide. [33] Mortality among TB patients co-infected with HIV is much higher than seen among those HIV uninfected TB patients. [33] Gauteng province was among the top of the provinces with the highest number of people infected with TB and second highest after Mpumalanga in the recent national DRTB survey. [2, 12, 48]

1.5.2 Decentralization of DRTB treatment

In SA, TB and especially DRTB remained a major public health challenge and the government had tried scaling up interventions and strategies that were to address this. [2, 12] Some of these strategies were to increase ART roll out for all patients with TB including those with DRTB and to decentralize the management of DRTB. Decentralization of DRTB treatment meant that all PHC facilities were to start providing treatment to all DRTB patients without referring them to a centralized facility for management.[2, 12] Decentralization was implemented in order to increase treatment coverage of DRTB patients and to reduce the time to initiation of DRTB treatment to less than 5 days after diagnosis of DRTB.[2] The SA DOH policy framework on managing DRTB stipulated that these patients needed to be managed closer to their homes in order for them to commence treatment as early as possible but also to improve adherence to the treatment.[2] Within this framework it was proposed that patients be treated outside of the traditional centralized facilities, as the incidence was rising and these facilities could not cope due to human resources among other reasons.

A meta-analysis done by Williams et al, looked at 27 high TB burden countries and concluded that higher treatment success rates were seen in patients managed in the community compared to hospitalized patients. [32] Access to treatment was improved by decentralized care models. The study also concluded that the strategies put in place in the communities to manage lost to follow up patients had a positive influence on treatment success. Feasibility of treating DRTB patients outside the centralized hospital setting has also been shown for resource constraint countries.[32] Weiss et al meta-analysis has shown that outcomes in community model of care had a success rate of 65%.[6] This is an average above that seen globally but they found no significant difference in this study for treatment success.[6, 33] Community based treatment of DRTB patients appeared to have adequate treatment outcomes as seen in Weiss et al and Williams et al. [6, 32] The same results were seen even in resource constrained settings.[4, 24, 36] Many studies looked at DRTB treatment outcomes from community based decentralized care models and lacked to investigate clinic based decentralized care models, particularly in urban

settings. An ambulatory care model in Indian slums in patients infected with HIV showed encouraging treatment outcome results. [36] This Indian study is the only one that investigated an ambulatory care model in DRTB patients co-infected with HIV.

Treating DRTB patients outside centralized facilities has been seen to be feasible and it has contributed to reduced treatment delays seen in the TB programmes and it has improved survival of these patients. [4]

1.5.3 DRTB Treatment outcomes

WHO reported that the proportion of patients diagnosed with MDRTB or any RRTB who achieved successful outcomes (cured and completed) was 54%, with 16% deaths, 30% lost to follow-up, 9% were treatment failure in 2017. [33] The lost to follow up rate has doubled since 2013. TB was among the top conditions causing death worldwide and caused more deaths than HIV by 2016. [33] TB accounted for additional deaths within the HIV co-infected population. [33]

Successful treatment outcomes in a meta-analysis by Williams et al (including studies from nine countries with a high TB burden), comparing community and hospital care models has shown better outcomes for community versus hospital care (68% vs. 57%).[32] Treatment failures were also lower in community compared to hospital-based treatment at 7% vs. 19%, although the HIV co-infection prevalence was low in these studies.[32] The mortality rate of patients with MDR/RR-TB in SA was reported to be around 20%.[12] SA aims to improve their DRTB success rate to 75% by end of 2022 according to the NSP goals. Despite reported good drug susceptible and DR-TB outcomes elsewhere in the world, DR-TB outcomes remained poor in SA, with success rates of below 60% in different settings. [14, 38, 40] The country has not yet achieved its DRTB treatment successful outcomes target of 75%, as stipulated in the National Strategic Plan.[10] This is threatening the control of TB in this country currently and in years to come if no improvements are made. For SA, WHO reported an estimation of MDR/RRTB treatment success to be 54% and 27% for XDRTB in 2017. [33] The picture seen in SA is testament to generally poor treatment outcomes in DRTB patients compared to drug susceptible TB. When we look specifically at the HIV infected population, the DR-TB treatment outcomes in other countries with a high HIV burden were better than those seen in SA.[23-25] South Africa is among countries in the world with high death rates and loss to follow up of DRTB patients.[33] Despite reported improved drug sensitive TB outcomes, treatment success rates remain poor among patients with MDR-TB, especially those co-infected with

HIV even with a high ART coverage, as we see in a study by Umanah et al, although this looked only at centralized care model.[40] In SA's community decentralised care models in the rural and peri-urban settings, showed better treatment DR-TB outcomes due to interventions that improved and supported the MDR-TB control programme.[4] In other countries a high cure rate was achieved, although sample size in some studies was small.[23, 25] The study by Isaakidis assessed treatment outcomes in an ambulatory model in an Indian slum setting in HIV co-infected patients, and showed comparable outcomes to other SA studies.[36] Treatment default of patients is a challenge in managing and controlling TB. Patients are lost due to the prolonged duration of treatment for DR-TB, side effects of the drugs, the injectable route of drug administration during IP, and in SA particularly financial and transport challenges fuel the poor control of DR-TB. [9] MDR-TB is treatable only if patients are given appropriate therapy and treatment is adhered to.

The Stop TB Partnership Global Plan estimates that 1 million cases of MDRTB need to be detected and started on treatment and achieve treatment success in over 75% of these cases.[11] There was only very few of the countries globally which were able to achieve this set treatment success target.[11] South Africa was still lagging behind its own target, and if appropriate interventions are no implemented, for example: full implementation and financial and human resource mobilization to support the decentralised management of MDR-TB, implement psychosocial support for these patients, shortening of treatment duration and limiting adverse events this target may not be achieved in the near future. SA plans to decentralise treatment and care to all primary health care facilities so that primary healthcare nurses start treating patients with DR-TB and initiate treatment within five days.

1.5.4 Time to unsuccessful treatment outcomes (death and default)

In different studies time to unsuccessful outcomes has shown to be very short, with many patients dying or defaulting within the first 6 months of treatment (intensive phase). [28, 37, 43] Median survival times for death outcome seen in a study by Isaakidis et al was the shortest at 27 days (range of 1 to 229 days) after DRTB treatment was started.[36] Kliiman et al study done in Estonia examined patients with MDRTB and XDRTB had a median time to death of 5 months,[28] whereas another study in Russia showed median time to death was just over 1 month.[43] Survival times of patients with DRTB showed similar times compared to a study done in Asia by Hoa et al on drug susceptible TB. Hoa et al examined time to unsuccessful outcomes in three Asian countries and found that half of the deaths occurred within the first 2

months of initiating TB treatment in Cambodia and 11 weeks in China and Vietnam although this study only examined drug susceptible TB [37] Hoa et al also examined the median time to default in the same study and it was 2 and 3 months in China and Cambodia/Vietnam respectively.[37] These findings are very pertinent as they raise a challenge that needs to be addressed for these patients especially within the first few months of initiating TB treatment.

1.5.5 Predictors of unsuccessful DRTB outcomes

Different studies have examined the predictors of poor outcomes in different settings and have found different demographic and clinical factors associated with poor outcomes. Among these factors male gender, older and younger age, previous history of TB, positive sputum smear, cavitatory diseases, low CD4 count and no ART initiation in HIV infected patients were some of the predictors of death and/or failure. [21, 28, 35]

Male gender was found to be a predictor of poor outcomes in a meta-analysis by Johnston et al. [35] In the same study, other predictors of poor outcomes were alcohol abuse, low BMI, smear positivity at diagnosis, fluoroquinolone resistance and XDR resistance pattern. [35] Brust et al showed that more baseline drug resistance and prior TB were independent risk factors for treatment failure.[21]

HIV has been associated with poor treatment outcome in different studies. [14, 21, 28] HIV co-infection with DRTB was a predictor for death and a predictor of default in a few studies. [14, 21, 37] Deaths due to TB in HIV co-infected patients remained high in this region compared to elsewhere, despite the massive Anti-Retroviral Therapy (ART) roll-out.[5, 14, 41] ART coverage in TB HIV co-infected patients remains low, despite the evidence that ART improve TB treatment outcomes with up to 86% reduction in mortality.[8, 10, 13] In SA only half of TB patients co-infected with HIV had been initiated on ART's in 2012.[5] For HIV co-infected individuals, initiating ART has shown to improve treatment outcomes in patients with MDR-TB.[13, 14] Initiation of ART in HIV co-infected patients during TB treatment in patients with MDR-TB was associated with a 86% reduction in mortality.[13] A study done in a SA centralised care model showed that timing of ART initiation was important in MDRTB patients, as it had an impact on mortality.[41] In the same study mortality was high among HIV co-infected patients who initiated treatment before MDRTB treatment was started, similar results shown in another SA study by Abdool Karim et al.[8] A study in Botswana has shown no difference in early MDRTB treatment outcomes, when looking at early culture conversion between HIV co-infected and HIV uninfected patients.[42] With these finding they concluded that the outcomes

may be comparable in similar settings. In HIV and TB co-infected patients, low CD4 count <100 increased mortality in DRTB co-infected patients in a study by Mohr et al. [62]

Previous history of TB treatment was found to be another independent predictor of poor outcomes. Urban residence has been shown to predict poor treatment outcomes for XDRTB patients in particular. [28] Kliiman et al also showed that having high grade smear positivity of DRTB was a risk factor for poor outcomes [28] Low baseline weight, <60kg and <45kg and a low body mass index (BMI) were also associated with higher hazards of death and/or treatment failure. [14, 24, 41] Integrated TB and HIV care services have shown to improve treatment outcomes. [8, 9, 19]

In a study done in SA, low haematocrit was a predictor of death, although this study was done before the SA national ART roll-out. [14] Severe anaemia was also a predictor of failure in a study by Umanah et al, which also associated co-morbid conditions like Diabetes mellitus (DM) with treatment failure. [41] Diabetes as a co-morbid condition was also associated with poor treatment outcomes in a study by Periasamy et al, although the sample size was very small. [34] In the same study smoking and patients diagnosed with pre-XDRTB were also predictors of poor outcomes. [34] Cavities on CXR at baseline were independent risk predictors of mortality in patients with HIV co-infection rate in SA centralized model. [41]

Health system factors have also been associated with poor outcomes. Some of these factors are cross-border management of patients in terms of the continuum of care and reporting of the treatment outcomes, financial support for these patients, and health care providers' ability to support and treat these patients holistically. [9, 17] Addressing these factors will improve treatment outcomes. A meta-analysis by Weiss failed to show any factors associated with treatment success. [6]

1.5.6 Summary of literature review findings:

DR-TB treatment outcomes are generally poor globally. There are good DR-TB outcomes from other countries but SA has shown outcomes that are below those of many countries, this may be due to lower HIV prevalence in these countries. SA has failed to achieve its target for successful DRTB treatment outcome of 75%. DR-TB decentralised care and treatment models have been widely documented and have shown improved outcomes compared to the centralised/hospitalized care models. The decentralized models of care have not been widely implemented in urban settings in SA wherein the population is highly mobile as seen in the

City of Johannesburg. MDR and XDR-TB treatment outcomes have been studied extensively but there is paucity of literature evaluating outcomes for any form of RR-TB other than MDR-TB and XDR-TB. Ambulatory care models in urban settings have not been broadly evaluated.

There was paucity of literature assessing time to unsuccessful DRTB outcomes. Time to unsuccessful DRTB outcomes was evaluated in only two studies, Isaakidis et al and Kliiman et al which reported very short survival times, with the median time to death of 27 days and 5 months respectively. [36, 43] Other studies evaluated survival times in patients with drug susceptible TB and the results showed similar findings of median times of 2 and 3 months. [37, 43] These findings are important as measures to improve survival of these patients need to be implemented especially during the IP of treatment.

Several predictors of poor outcomes have been reported in many studies and these included some demographic characteristics for example being male gender, advanced or younger age and smoking history. [21, 28, 29] Clinical characteristics associated with poor outcomes were higher baseline resistance, smear positivity, previous TB treatment, baseline cavitatory disease, HIV co-infection with low CD4 count and not initiated on ART. Co-morbid conditions like DM were also independent predictors of unsuccessful outcomes. Low body weight <45kg and <60kg and BMI were some of the predictors found in different studies.

1.6 Study Aims and Objectives

1.6.1 Aim of the study

To evaluate DR-TB treatment outcomes and to determine the predictors of these outcomes.

1.6.2 Study Objectives

1. To describe all RR-TB treatment outcomes: treatment success (cured and completed), unsuccessful treatment outcomes (died, treatment failure and lost to follow-up) and transfer out.
2. Assess any differences in outcomes between HIV positive and negative patients
3. To describe time to unsuccessful treatment outcomes (death and defaulted).
4. To assess the predictors of death, default and overall unsuccessful treatment outcomes.

2. CHAPTER 2: METHODOLOGY

2.1 Introduction

This chapter reviews the study design, study population and setting and selection of the study site, sampling and selection of the patient population, measurements and data sources. Also discussed in this chapter are key definitions, data management and analysis, and ethical considerations.

2.2 Study design:

A retrospective study design using secondary data of patients' records was used to analyse routinely collected data. The data were extracted from the clinic's database, at the DR-TB outpatient clinic at CMJAH covering the period from 1stJanuary 2010 to 31stJanuary 2014.

2.3 Study setting:

CMJAH is one of the two tertiary (academic) hospitals located in the inner City of Johannesburg (COJ). The outpatient TB clinic at CMJAH is a specialist clinic which serves as a referral site for complicated TB cases and any DR-TB patients from feeder primary healthcare centres. It is an urban decentralised specialist DR-TB clinic. The clinic started operating in 2010 as a decentralised ambulatory DR-TB site which serves as a referral centre for PHC in the inner city of Johannesburg. The clinic enrolled any patient with DRTB except those who came with XDRTB and smear positive MDRTB

2.4 Study population:

The study population consisted of patients diagnosed with any RR-TB and enrolled into care at the CMJAH TB focal point between 1st January 2010 and 31st January 2014.

2.5 Study sample:

A total of 335 patients with any form of Rifampicin resistant TB diagnosed during the period January 2010 to January 2014 found in the database were included in the study. The following criteria was used to ensure appropriate selection of patients into the study.

2.5.1 Inclusion criteria:

Patients included in the study were:

- 18 years and above

- Laboratory diagnosis of any Rifampicin resistant TB
- Started treatment at the CMJAH DRTB outpatient clinic.

2.5.2 Exclusion criteria:

- TB cases with drug susceptible (sensitive) TB
- Non-tuberculous mycobacteria (NTM) or otherwise known as mycobacteria other than TB (MOTT)
- Other mono-resistant TB other than Rifampicin
- Patients under the age of 18 years
- Patients who were enrolled outside the study period.

2.6 Data source and measurement:

2.6.1 Data collection and procedures:

As part of the clinic's routine care, data in the clinic were collected routinely from clinical records of patients and data entered in the TB Focal Point Access database. The data clerks routinely transferred data from the clinical records into the MS Access database as part of normal day to day record keeping and management. Data were updated at every patient visit. Patients' demographic information were collected by the clerks whereas the clinicians collected clinical history as part of routine care.

As part of routine care, HIV counselling and testing was offered to all patients where status is unknown or negative previously. HIV rapid testing were done and if positive a laboratory HIV Enzyme Linked Immuno-sorbent Assay (ELISA) confirmation done. CD4 counts were done in all HIV positive patients. No baseline VL were done, as recommended by the SA HIV management guidelines. Patients not already on ART were initiated on ART within 2 to 8 weeks of starting anti-TB drugs, unless they refused treatment. Decision to initiate ART was based on CD4 count below 350 cells/mm^3. This was later followed by a guideline change in management for all TB patients to start ART irrespective of CD4 count at a later stage. Patients received their ARTs and anti-TB drugs at the same clinic for the duration of TB treatment for better management of both diseases.

Patients diagnosed at the feeder clinics with any form of DRTB on sputum XPert® MTB/RIF were referred to CMJAH TB clinic for further management and initiation of therapy. On enrolment at the CMJAH TB clinic, patients were registered, examined and sputum collected

for confirmation of type of resistance. Confirmation of the results were done using Line Probe Assay (LPA) and culture and drug sensitivity testing (DST) for first and second line TB drugs. These tests were done by the National Health Laboratory Services (NHLS). The culture and DST done by NHLS used liquid media such as BACTEC Mycobacterial Growth Indicator Tube (MGIT) 960 and Becton Dickinson.

Drug Resistant TB treatment regimen used:

Most patients in the clinic were initiated on standardized 5 drug combination anti-TB treatment and were treated for a maximum of 18 to 24 months. Some patients initiated were initiated on individualized regimes due to varying reasons, for example prior to 2012 there were no standardized DRTB treatment guidelines. Individualized treatment regimens were also given in patients who had or developed adverse drug reactions and those with co-morbid conditions like renal failure or psychosis. Patients on a standardized regimen, were initiated on a combination of Kanamycin (KM) or Amikacin (AM) injectable, Terizidone (TDZ), Moxifloxacin (MFX), Ethionamide (ETO) and Pyrazinamide (PZA) during the intensive phase of therapy which was at least 6 months. Injectable treatment was stopped after the IP of therapy when TB cultures have been negative. Treatment was taken daily except the injectable which was taken for 5 days per week during the intensive phase. Injectable treatment was administered by a nurse at their local PHC facility near where they resided, this also facilitated DOTS for these patients by their local PHC nurses. Patients who were too ill to warrant hospital admission, any smear positive DRTB were referred to the centralized facility at STDIH for admission or further management.

Clinicians continued to monitor patients' monthly for clinical progress, adverse events, sputum smear and cultures and DST, CXR and any other new medical conditions until 1 year after completion of therapy. The clinic had a dedicated sputum collection nurse ensured that all patients' sputum samples were collected at all their clinic visits.

The following data were collected as part of routine care at the facility:

Demographic data: Included gender, age, employment history, referral facility and citizenship.

Clinical data: Included baseline weight, site of TB, ART's, RR-TB diagnosis, date of starting TB treatment, treatment outcomes (cure, completed, default, died, failed and transferred-out)

and date of outcome and co-morbid conditions (Diabetes, liver disease, renal failure, Epilepsy). Baseline weight was done for all patients.

Laboratory data: Included blood and sputum test results.

Blood tests: HIV status, CD4 count, viral load, urea, electrolytes and creatinine, thyroid function tests, haemoglobin and liver function tests.

Sputum tests: Included Xpert® MTB/RIF, smear (AFB), line probe assay, microscopy, cultures and DST.

As part of this study, the hospital's Resistant TB focal point database was searched for all the patients who were enrolled from January 2010 to January 2014 with any RR-TB diagnosis. data were extracted for this analysis in August 2015. For this study only data of interest to the analysis were extracted from the database.

Below are data variables that were extracted and used in the analysis for this study:

2.6.2 Treatment outcome variables:

The outcomes variables assessed were successful, unsuccessful and transfer out. Successful outcomes included cured and completed treatment. Unsuccessful outcomes included death, treatment failure and lost to follow-up. WHO DRTB treatment outcome definitions were used together with the South African Department of Health Drug-resistant TB Policy Guidelines 2013.

Outcome variables and definitions:

1. Cured - treatment completed without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient will still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

2. Completed treatment - treatment completed without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.

3. Treatment success –the sum of those who were cured plus those who completed treatment.

4. Default – a patient whose treatment was interrupted for two consecutive months or more.

5. Transfer out was defined as all whose care was transferred to other healthcare centres treating DR-TB. This did not include those patients transferred immediately to STIDH.

6. Treatment failure - treatment terminated or need for permanent regimen change of at least two anti-TB drugs due to: lack of conversion by the end of the intensive phase; or bacteriological reversion in the continuation phase after conversion to negative; or evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs and due to adverse drug reactions.

7. Died (All-cause mortality) – a patient who died for any reason during the course of treatment.

8. Unsuccessful outcome – a sum of died, default and failures.

9. Still on treatment – patients who at the end of this study period were still taking their TB medications.

2.6.3 Exposure variables:

1. Socio-demographic variables:

    - Age: patients' age in years at time of starting TB of treatment
    - Gender: gender of patient (male or female)
    - Nationality: SA or non-SA
    - Employment: employed or unemployed at time of starting TB treatment
    - Education level: patients' education level (education or no education)
    - Referral site: health facility where patient was referred from.

2. Clinical and laboratory variables:

    - Weight: body weight at time of starting treatment

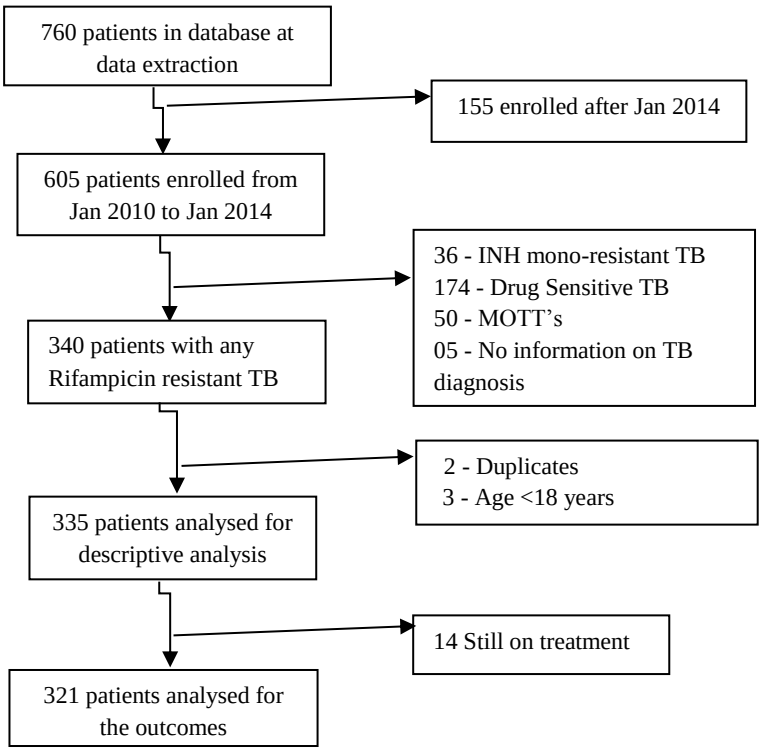
- TB diagnosis: laboratory diagnosis/type of TB resistant strain (MDR, XDR, RMR, XDR, RR not confirmed by DST/LPA)
- Site of TB: pulmonary or extra-pulmonary
- HIV status: HIV diagnosis of patient (negative or positive)
- CD4 count: CD4 at baseline (CD4 <200; 200-350; 350-500 and >500)
- ART: patient on ART or not on ART at time of outcome
- History of previous TB: New, Retreatment after 1st line default/failure and Retreatment after 2nd line default/failure
- Comorbid conditions: Diabetes Mellitus, Epilepsy, Liver disease, Renal insufficiency

2.7 Data Management

Data were entered in the clinic on a MicroSoft Access database. For any missing data, the patient records were used to correct and update the database. Data were exported into STATA version 12.0 for data cleaning and analysis. Data cleaning was done by excluding patients not eligible for the study according to the exclusion criteria, and removing unwanted variables that were not important for this study objectives. Missing data were assessed for all variables important for the analysis.

A total of 760 patients were ever enrolled to CMJAH TB clinic at the time of data extraction by August 2015. Patients who were enrolled between January 2010 and January 2014 were 605 (80% of ever enrolled to clinic). Of these 605 patients; 375 (61%) had any Rifampicin drug resistant TB, 36 (6%) had INH mono-resistance, 50 (8%) had MOTTs, 174 (28%) had drug sensitive TB and 5 (0.8%) had no information on TB diagnosis. These patients with INH mono-resistance, sensitive TB, MOTTs and those without information on TB diagnosis were excluded from the study (see Figure 1). Duplicates and those aged below 18 years (5 observations) were excluded from analysis. All 335 patients were analysed during the descriptive analysis, but only 321 patients were analysed for the outcomes measure, due to 14 of them being on treatment at time of data extraction. Outcome measures of 5 patients were recorded under the wrong variable and were changed, which included 3 deaths and 2 defaulted patients' outcome measures recorded under outcome variable "Other".

Fig 1: Flow chart illustrating participants analysed for Drug Resistant TB outcomes.



Age, weight and CD4 count were analysed as both continuous and/or categorical variables. Age was categorized into 2 groups <40 years and >40 years; weight (<50kg, 50-59kg, 60-70kg and >70kg); and CD4 count grouped (<200 cell/mm^3, 200-350 cell/mm^3, 350-500 cell/$mm^3$and >500 cell/mm^3). This was done to avoid confounding which may be seen when these data are modelled as continuous variables. One patient was recorded to be on ART yet HIV negative, so CD4 count was not analysed. A total of 5 patients had their weight below 29kg which were highly likely to be wrong for an adult patient and therefore were assumed to be missing and not analysed (5 observations). Normality of continuous data was assessed using histograms, quantile plots, and skewness and kurtosis were evaluated. Shapiro Wilk test was also used to assess for normality of continuous variable. New variables which were necessary for analysis were generated from existing variables in the dataset. The new DRTB duration variable was generated. Person times were calculated from the date of DRTB treatment start date and date of outcome. For time duration to final outcome, dates which created a negative time were excluded from the analysis. Categorical variables with sparse observations were merged, for example nationality into SA and non-SA. Education was also merged into Education and No Education. For retreatment patient category, data were merged into 2 groups, namely retreatment after regimen 1(default/failure with regimen 1) and retreatment after regimen 2 (default/failure with regimen 2). For diagnosis DRTB categories, Poly-resistant TB and

XDRTB categories were merged with MDRTB category due to very small number of patients (less than 5) within these two categories.

Outcome measures were stratified by HIV status. New outcome variables were generated for outcome, namely successful and unsuccessful.

2.8 Data analysis:

2.8.1 Descriptive and Inferential analysis

Proportions and frequencies were used to describe all categorical baseline and clinical variables in the data. Distribution tables were used to demonstrate demographic and clinical data. Continuous variables were described by their mean and standard deviation if they were normally distributed; and by a median and interquartile ranges if the data were skewed. Normally distributed continuous data were displayed using histograms. Both demographic and clinical data were described and compared between the different outcome measures. Outcomes measures were analysed separately then categorized into successful (the sum of cured and completed treatment), unsuccessful (treatment failure, died, lost to follow up) and transfer out. Differences in the outcomes were compared by HIV status. Equality of proportions between HIV negative and HIV positive patients was analysed to show the effect of HIV on treatment outcomes. Kaplan-Meier survival estimates were used to estimate survival times. Median and interquartile ranges were used to describe survival times.

2.8.2 Univariable and Multivariable analysis

The predictors were only determined for unsuccessful outcomes. Univariate Cox regression models were used to estimate crude hazards ratios of the predictors associated with both death and default separately, and then combined for unsuccessful outcomes. Multivariate Cox regression models were used to estimate the adjusted hazards ratios. All covariates with p-value less than 0.1 from the univariate models were selected into the multivariate models. For the Cox regression, the Efron's approximation method for ties which is more accurate than the Breslow's method (being the default used in Stata survival analysis) was used. Priori biologically plausible covariates considered important were also included in the multivariable regression analyses.

2.8.3 Model diagnostics

Goodness of fit of the final model were tested (Appendix 4).

2.9 Ethical Considerations

Ethics approval to conduct this study was sought from the Wits University Human Research Ethics Committee (HREC), see attached Appendix 6. Permission to use the hospital's database was also sought from the CEO of CMJAH, also attached in Appendix 5. Identifying information from the database was removed during data extraction, and the use of unique identifiers employed.

3. CHAPTER 3: RESULTS

3.1 Introduction:

In this chapter the results are presented according to the study objectives and the analysis plan. This includes: demographic, clinical characteristics, time to treatment, successful outcomes and unsuccessful treatment outcomes, and predictors of poor treatment outcomes are presented.

3.2 Baseline demographic characteristics of participants

Table 1.1 below shows a description of demographic characteristics of the patients with any RR-TB. Among the 335 patients diagnosed with any RRTB, 52.5% of them were female. Median age in the study was 34 years. The study observed that DRTB was diagnosed more in patients older than 40 years of age. Only 15.5% of the patients had a history of having attained some level of education. Unemployment rate was 22.5% among those where history of employment was known. Majority of the patients 97.3% were SA citizens. 86% of the patients were referred from PHC facilities.

Table 1.1: Baseline Demographic Characteristics of all RR-TB Patients at CMJAH from January 2010 to January 2014.

Characteristics	**Level**	**N (%) (N=335)**
Age (years)	*34 (18 – 81)	
	<40	229 (68)
	>=40	106 (32)
Gender	Male	159 (47.5)
	Female	176 (52.5)
Nationality	South African	326 (97.3)
	Non-SA	9 (2.7)
Employment	Employed	51 (15.2)
	Unemployed	82 (24.5)
	Unknown	196 (58.5)
	Missing	6 (1.8)

Education	Education	52 (15.5)
	No Education	74(22.1)
	Missing	209 (62.4)
Referring facility	Primary Healthcare	288 (86.0)
	Private facility	3 (0.9)
	CMJAH wards/speciality OPD	25 (7.5)
	Other hospital	9 (2.7)
	Missing	2 (0.6)

= Number %= Percentage * = Median (Inter-quartile range)

3.3 Baseline clinical characteristics

Table 1.2 below shows baseline clinical characteristics of the patients in this study. The study observed that the number of patients being diagnosed for the first time with DRTB found in this study was high, with 71.9% of patients having no prior history of TB. Approximately only a third of the patients in this study had a previous TB treatment prior to being diagnosed with DRTB, 79 (23.6%) were retreatment after failing regimen 1 and 15 (4.5%) were TB retreatment or failing regimen 2. Majority of the patients in this study were diagnosed with confirmed Rifampicin mono-resistant TB (34%) and MDRTB at 26.9%. The prevalence of poly-drug resistance and XDRTB was 1.5%. The remaining 37.6% of patients were Rifampicin resistant diagnosed on GeneXpert only, without any confirmation by either culture or LPA. We observed that 96.9% of the patients in this study presented with pulmonary disease. The baseline smear positivity rate in the study was 58.5%. GeneXpert testing of sputum identified 20 more patients (6% more) with DRTB than sputum smear test alone. Half of the patients presented with symptom of a cough, night sweats in 127 (38%) patients, chest pains in 95 (28.4%), weight loss in 90 (27%) and appetite loss in 54 (16.2%).

Of the 335 patients, all except 1 had known HIV status (99.7%). The clinic had a very high uptake of HIV counselling and testing. There was a very high HIV/TB co-infection rate of 82.9%. Among the 277 HIV co-infected patients, the ART coverage was 79.5%. Median CD4 count was 142 cells/mm^3 (IQR: 3 - 835). Of the 277 HIV infected patients baseline VL results

were recorded for only 27 (9.7%) patients, with only 4 of these virally suppressed. Only 42 (15.3%) HIV co-infected patients were receiving Co-trimoxazole prophylaxis.

Recording of CXR findings was low. CXR findings were recorded in only 113 (33.7%) of the patients and found to be abnormal in 24 (26.2%) of these patients. These CXR findings showed 14 (13.1%) bilateral infiltrations, 5 (1.5%) cavitatory disease, 2 (0.6%) patients had pleural effusion and 5 (1.5%) had a combination of cavities, infiltrations and hilar adenopathy. Of the 10 extrapulmonary TB patients, ultrasound showed 3 abdominal TB and 4 cardiac TB.

The presence of co-morbidities was minimal (5.4%) in the study, 6 (1.8%) patients had Diabetes Mellitus, 5 (1.5%) had Epilepsy, 4 (1.2%) had Hepatitis (cause not specified), 2 (0.6%) had renal failure, 1(0.3%) had a psychiatric condition not specified. There were 3 pregnant women among this cohort.

Table 1.2: Baseline Clinical Characteristics of DR-TB Patients at CMJAH from January 2010 to January 2014.

Factors	Level	N=335 (%)
DRTB Diagnosis	MDRTB	90 (26.9)
	Rifampicin-mono resistant (LPA and/or DST)	114 (34.0)
	Rifampicin-resistance on GXP (no confirmation done)	126 (37.6)
	Poly-resistant TB	4 (1.2)
	XDR-TB	1 (0.3)
Baseline sputum Smear	Positive	196 (58.5)
	Negative	139 (41.5)
Baseline sputum GeneXP	Positive	216 (64.5)
	Negative	119 (35.5)
Presenting symptoms:	Chronic cough	
	Yes	167 (49.9)
	No	168 (50.1)
	Night sweats	
	Yes	127 (38)

	No	207 (61.8)
	Missing	1 (0.2)
	Chest pains	
	Yes	43 (13)
	No	292 (87)
	Weight loss	
	Yes	90 (27)
	No	243 (72.5)
	Missing	2 (0.5)
	Loss of appetite	
	Yes	54 (16.2)
	No	279 (83.2)
	Missing	2 (0.6)
	Dyspnoea	
	Yes	21 (6)
	No	314 (94)
	Fever/rigors	
	Yes	29 (9)
	No	301 (90)
	Missing	5 (1)
	Haemoptysis	
	Yes	7 (2)
	No	328 (98)
	Lymphadenitis	
	Yes	2 (1)
	No	331 (98
	Missing	2 (1)
History of TB	New	240 (71.9)
	Retreatment after/failing Reg1	79 (23.6)
	Retreatment after/failing Reg2	15 (4.5)
	Unknown	1 (0.3)
HIV status	Positive	277 (82.7)
	Negative	57 (17.0)
	Missing	1 (0.3)

HIV+ CD4 cell count Category:	 *142 (23 - 388) <200 200 – 350 350 – 500 >500 Missing	n=277 140 (50.5) 42 (15.2) 26 (9.4) 9 (3.2) 60 (2.2)
HIV+ on ART	 Yes No	n=277 220 (79.5) 57 (20.5)
HIV+ Cotrimoxazole prophylaxis	 Yes No Missing	n=277 4 (1.4) 233 (84.1) 34 (12.5)
Site of TB	 PTB EPTB	 325 (96.9) 10 (3.1)
Weight (kg)	*54.3 (31.2 – 92.4) <50kg 50-59kg 60-70kg >70kg	 103 (34.0) 116 (38.3) 58 (19.1) 26 (8.6)
CXR	 Infiltrations Yes No Cavitations Yes No Pleural effusion Yes No	 14 (4.2) 321 (95.8) 8 (2.4) 327 (97.6) 2 (0.6) 333 (99.4)
Co-morbid conditions	Diabetes Mellitus Yes No Missing Epilepsy Yes	 6 (0.8) 333 (99.0) 1 (0.2) 5 (1.4)

	No	329 (98.3)
	Missing	1 (0.3)
	Renal insufficiency	
	Yes	2 (0.6)
	No	331 (98.8)
	Missing	2 (0.6)
	Hepatitis	
	Yes	4 (1.2)
	No	330 (98.5)
	Missing	1 (0.3)

= Number %= Percentage *=Median (Interquartile range)

3.4 Description of DRTB treatment outcomes

Overall, 64 (19.9%) patients had successful outcomes: 17 (5.1%) were cured and 47 (14%) completed treatment. Of the 122 (36.4%) patients with unsuccessful treatment outcomes, 30 (9%) had died, and we observed a high defaulter rate of 27.5% (92 patients). The remaining 135(40.3%) patients were transferred out. Patients who were still on treatment were 14 (4.2%). There were no treatment failures in this cohort.

3.5 Time to unsuccessful outcomes

Table 2.1 shows a summary of survival time to default and death (unsuccessful) outcomes. The study showed that defaulting happened early after initiation of treatment. The median time to default was 3 months (IQR: 1.4-8.5) with a defaulter rate of 0.2 per month. Deaths also occurred early after treatment initiation; results showed that among those who died, the median time of survival after starting treatment was 4.6 months (IQR: 0.9-13.8) with an incidence rate of 0.1 death per month. The overall median time to unsuccessful outcome (death and defaulters combined) was 3.2 months (IQR: 1.4-9.2). See Figures 2 and 3 below.

Table 2.1: **Summary measures of time to unsuccessful outcomes**

Unsuccessful outcome	Time at risk	Incidence rate	N	Survival time in months		
				25%	50%	75%
Defaulted	568.6	0.16	92	1.4	3	8.5
Died	188.3	0.14	30	0.9	4.6	13.8
Total	756.8	0.15	122	1.4	3.2	9.2

Figure 2: Probability of survival of patients with unsuccessful treatment outcomes (death and default) treatment outcome stratified by DRTB diagnosis among DRTB patients at CMJAH 2010-2014

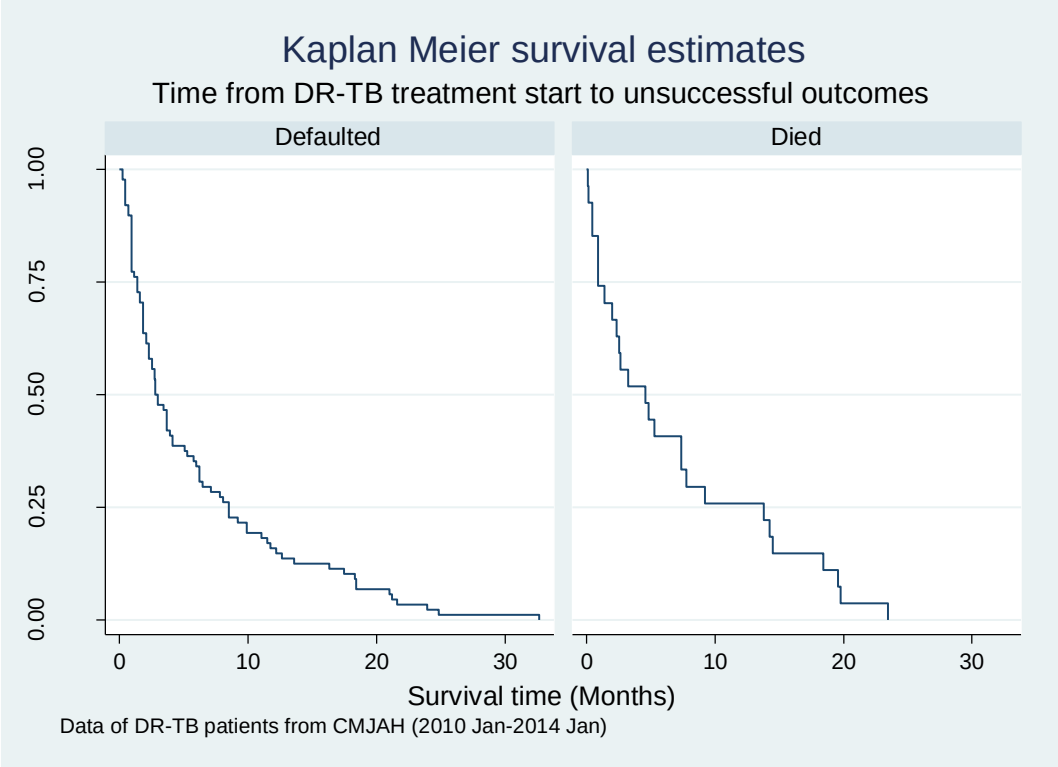
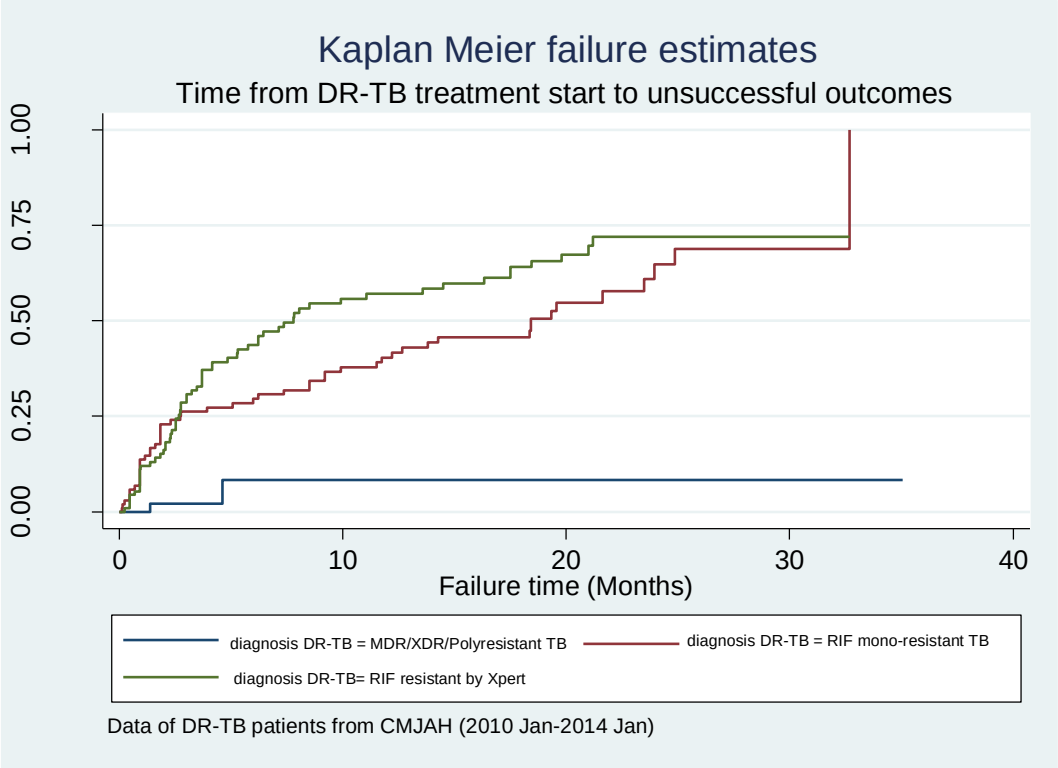


Figure 3: Probability of survival of patients with unsuccessful (death and default) treatment outcome stratified by DRTB diagnosis among DRTB patients at CMJAH 2010-2014



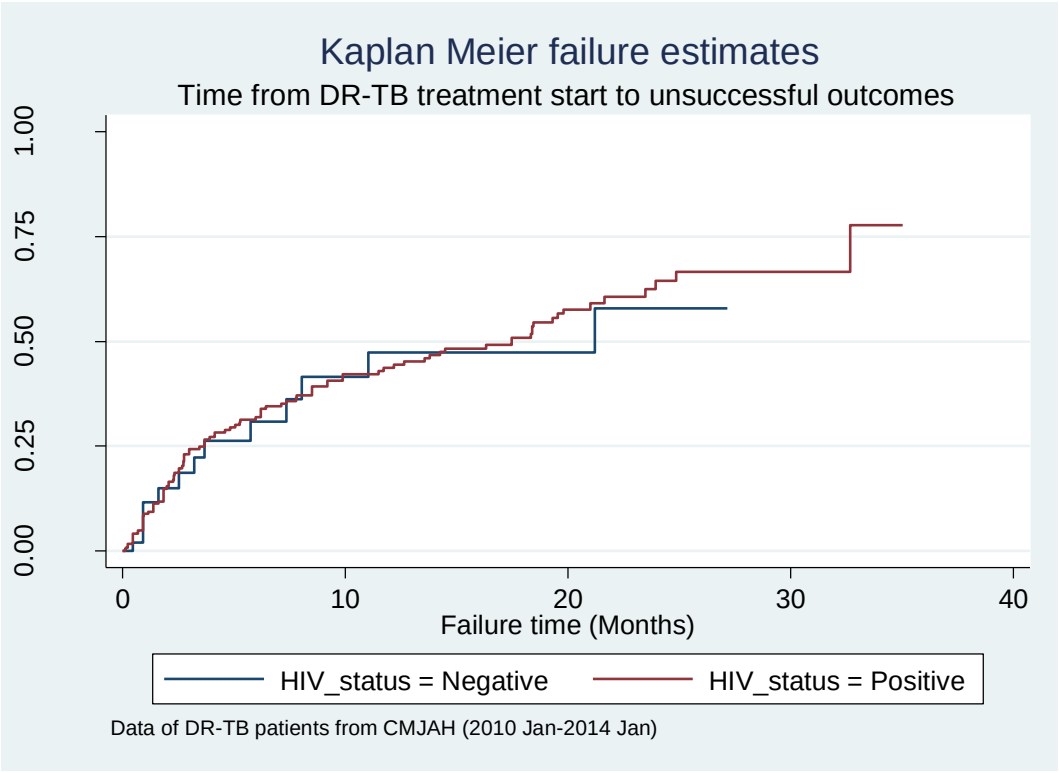
3.6 Treatment outcomes by HIV status:

Table 2.2 below shows the difference in proportions between HIV infected and HIV negative patients in the study. There was a statistically significant difference (p=0.002) between the proportion of HIV positive and HIV negative patients who were Transferred out. More HIV co-infected patients 101 (75%) were transferred out compared to 34 (25%) HIV negative patients. A high proportion of HIV positive patients died (27 (90%)) compared to HIV negative patients (3 (10%)), although this was not statistically significant (p=0.26). There was only one patient with an unknown HIV status. There was no significant difference in proportions between HIV co-infected and HIV negative patients for successful and unsuccessful outcome.

Table 2.2: **Comparison of DR-TB treatment outcomes by HIV status.**

DR-TB Treatment Outcomes		*HIV status N (%)*		
		Positive	***Negative***	**P-value**
		N=264(82.50)	***N=56(17.50)***	
Successful	**Completed**	41 (87.23)	6 (12.77)	0.3551
	Cured	16 (94.12)	1 (5.88)	0.1951
Unsuccessful	**Defaulted**	79 (86.81)	12 (13.19)	0.2005
	Died	27 (90.0)	3 (10.0)	0.2561
	Transferred out	101 (74.81)	34 (25.19)	0.0020

Figure 4: Probability of survival of DRTB patients by HIV status at CMJAH 2010-2014.



3.7 Predictors of death:

3.7.1 Univariable Cox regression model:

Patients diagnosed with Rifampicin resistant TB only with GXP (without confirmation by culture/LPA) had six times the hazard of death compared to those diagnosed with MDR/XDR/Poly-TB (HR=6.3; 95% CI:0.8-47.8; p=0.07) but this difference did not reach statistical significance. Very wide CI are noted and this may be attributed to the small sample size that could not show any significant difference. See Table 3.1.

3.7.2 Multivariable Cox regression model:

Table 3.1 below shows predictors of death. There were no statistically significant predictors of death and this result may be due to small sample in this study to show significant difference. Patients diagnosed with Rifampicin resistant TB by GXP only had six times the hazards of death compared to those diagnosed with MDR/XDR/Poly-TB (aHR=6.4; 95% CI:0.8-48.4; p=0.07) although statistical significance was not reached. A wide confidence interval is noted and this may be as a result of the small sample size.

Table 3.1: Predictors of death among patients with any RRTB at CMJAH between Jan 2010 to Jan 2014

Variables		Unadjusted Cox regression analysis				Adjusted Cox regression analysis			
		Hazard Ratio	P-value	95% Confidence Interval		Hazard Ratio	P-value	95% Confidence Interval	
Gender	**Female**	Ref							
	Male	1.053	0.894	0.494	2.242				
Age category	**<40 years**	Ref							
	>=40 years	1.293	0.513	0.598	2.793				
DR-TB Diagnosis	**MDR/XDR/Poly-resistant TB**	Ref				Ref			
	RIF mono-resistant TB	2.97	0.306	0.369	23.917	2.965	0.307	0.369	23.851

	RIF resistant by GXP	6.276	0.076	0.825	47.765	6.359	0.074	0.836	48.365

3.8 Predictors of treatment default:

Statistically significant predictors of default (negative predictors) seen in this study were: HIV infected not initiated on ART, baseline weight loss, Rifampicin mono-resistant TB diagnosis and Rifampicin mono-resistant TB diagnosis by GXP only.

3.8.1 Univariable Cox regression model:

Patients diagnosed with Rifampicin mono-resistance and those with Rifampicin resistance on GXP (unconfirmed) had statistically higher hazards of defaulting (HR=15.5; 95% CI 2.1-113; p=0.01) and (HR=18.2; 95% CI: 2.5-132; p=0.001) respectively, compared to those diagnosed with MDR/XDR/Poly-TB. The sample of patients diagnosed with MDR/XDTB was small and a possible reason for very wide CI's noted. Patients with baseline weight loss had twice the hazards of default than those without weight loss (HR=1.7; 95% CI: 1.1-2.7; p=0.03) and this was statistically significant (see Table 3.2). Among the HIV co-infected subgroup (Table 3.4), being on ART had 70% less hazards of default compared to not being on ART with HR=0.3; 95% CI: 0.19-0.6; p=0.001. HIV co-infected patients aged >40 years had 40% less hazards of default compared to those aged <40years but this did not reach statistical significance (HR=0.6; 95% CI 0.4 – 1.0; p=0.06). Being a non-SA citizen had two times higher hazards of default than being a SA citizens, but also did not reach statistical significance (HR=2.2; 95% CI: 0.6-6.8; p=0.19). (See Table 3.2 below).

3.8.2 Multivariable Cox regression model:

Patients with confirmed Rifampicin mono-resistance had fifteen times the hazards of default compared to those with MDR/XDR/poly-resistant TB (aHR=15.9; 95% CI:2.1-116; p=0.006) adjusting for weight loss. The hazards of default for those diagnosed with Rifampicin resistance by GXP only were seventeen times more than those diagnosed with MDR/XDR/poly-resistant TB (aHR=17.2; 95% CI 2.4-125; p=0.01), adjusting for weight loss. This finding may be due to patients who were having other resistance patterns being treated as if MDRTB and not getting adequate or appropriate therapy, that led to patients' not getting better and defaulted. Compared to patients with no baseline weight loss, those with baseline weight loss had 1.6 higher hazards of default (aHR=1.6; 95% CI 0.9-2.5; p=0.057), although this was not statistically significant when adjusted for DRTB diagnosis. See Table 3.2 below.

For the subgroup of patients with HIV co-infection (see Table 3.4 below), ART initiation decreased the hazards of defaulting by 87% (HR=0.13; 95% CI: 0.05-0.28; p=0.0001) when adjusted for TB Resistance diagnosis. ART initiation in co-infected patients was seen to be protective factor against default in this cohort of RRTB patients. Those diagnosed with Rifampicin monoresistance and those with Rifampicin resistance diagnosed only by GXPert had 10.8 and 10.5 times higher hazards of death compared to those diagnosed MDR/XDR/Poly-resistance TB, respectively when adjusted for ART initiation. These results are unexpected and may be that patients only diagnosed by GXPert without any confirmation by LPA/culture may have either MDR/XDRTB that was missed as a result of not confirming the diagnosis appropriately. Among the HIV co-infected patients, the positive predictor of default was being initiated on ART initiation, and negative predictors were Rifampicin monoresistance and Rifampicin resistance diagnosed only by GXP.

Table 3.2: Predictors of default among patients with any RRTB at CMJAH between Jan 2010 to Jan 2014.

Variables		Unadjusted Hazard Ratio	P-value	95% Confidence Interval		Adjusted Hazard Ratio	P-value	95% Confidence Interval	
Gender	**Female**	Ref							
	Male	0.711	0.11	0.467	1.081				
Age category	**<40 years**	Ref							
	>=40 years	0.640	0.067	0.398	1.031				
Diagnosis DR-TB	**MDR/XDR/Poly-resistant TB**	Ref							
	RIF mono-resistant TB	15.53	0.01	2.128	113.289	15.95	0.006	2.183	116.513
	RIF resistant by GXP	18.19	0.00	2.501	132.288	17.21	0.01	2.364	125.268
	No	Ref				Ref			

Weight loss	**Yes**	1.698	0.026	1.1	2.706	1.580	0.057	0.986	2.532

3.9 Predictors for unsuccessful outcomes (default and death combined):

Predictors of unsuccessful outcomes were confirmed Rifampicin mono-resistance diagnosis, Rifampicin resistance by GXP diagnosis. See Table 3.3 below.

3.9.1 Univariable Cox regression model:

Not initiated on ART had 3 times higher hazards of unsuccessful outcomes in HIV positive patients (HR=2.6; 95% CI: 1.6-4.4; p=0.000). For every unit increase of weight, there was 2% less hazards for unsuccessful outcomes (HR=0.98; 95% CI: 0.96-0.99; p=0.04), see Univariable model in Appendix 2. Patients with confirmed Rifampicin mono-resistance and those with Rifampicin resistance by GXP only had 9 times the hazards (HR=9.2; 95% CI: 2.2-38.1; p=0.002) and 12 times the hazards (HR=12.3; 95% CI: 3.0-50.5; p=0.0001) of unsuccessful outcomes respectively, compared to those with MDR/XDR/poly-resistant TB. Wide CI are noted in the results and this may be due to the small sample. Patients with body weight <50kg had 1.5 times higher hazards of unsuccessful outcomes (HR=1.5; 95% CI: 0.9-2.4; p=0.06) compared to those with weight above 50kg, although the difference was not statistically significant at 5% significance level.

3.9.2 Multivariable Cox regression model:

Patients with confirmed Rifampicin mono-resistance diagnosis had 8 times the hazards (aHR=8.5; 95% CI: 2.0-35.2; p=0.003) and those with Rifampicin resistance by GXP only diagnosis had 11 times the hazards (aHR=10.8; 95% CI: 2.6-44.8; p=0.001) when compared to those diagnosed with MDR/XDR/Poly TB. This finding of very high hazards of unsuccessful outcomes for patients diagnosed by GXP only, may be due to patients having other and extensive resistance patterns being treated as though they were MDRTB or RRTB and not receiving adequate and appropriate therapy, that led to patients not responding to treatment and achieving poor outcomes. There are very wide CI, highlighting the small sample size in the study. See Table 3.3 below.

Table 3.3: Predictors of unsuccessful outcomes (died and default combined) among patients with DRTB at CMJAH between Jan 2010 to Jan 2014.

Predictors		Univariate analysis				Multivariable analysis			
		Unadjusted Hazard Ratio	P-value	95% confidence Interval		Adjusted Hazard Ratio	P-value	95% Confidence Interval	
Gender	**Female**	Ref							
	Male	0.778	0.179	0.540	1.122				
Age category	**<40 years**	Ref							
	>=40 years	0.767	0.196	0.514	1.146				
DR-TB Diagnosis	**MDR/XDR/Poly TB**	Ref				Ref			
	RIF monoTB	9.236	0.002	2.237	38.129	8.460	0.003	2.032	35.219
	RIF resistant by GXP	12.319	0.0001	3.004	50.518	10.865	0.001	2.636	44.774
Weight category	**51-59 kg**	Ref				Ref			
	<50 kg	1.524	0.066	0.972	2.388	1.561	0.056	0.989	2.463
	60-70 kg	1.007	0.98	0.572	1.774	0.931	0.808	0.523	1.658
	>70 kg	0.931	0.848	0.448	1.934	0.956	0.905	0.455	2.007

3.10 Predictors of unsuccessful outcomes among HIV positive patients:

Among HIV co-infected patients, negative predictors of default were diagnosis of confirmed Rifampicin mono-resistance and those with Rifampicin resistance diagnosed by GXP only (see Table 3.4). Being initiated on ART was a positive predictor of default among HIV co-infected patients. Among the HIV co-infected patients, being initiated on ART reduced the hazards of default by 87% (aHR=0.13; 95% CI: 0.05-0.3; p=0.0001) compared to those not initiated on ART, when adjusted for DRTB diagnosis. Both groups of patients with

confirmed Rifampicin mono-resistance diagnosis and Rifampicin resistance by GXP only diagnosis had 11 times higher hazards of default (aHR=10.8; 95% CI:1.4-84; p=0.02) and (aHR=10.6; 95% CI:1.4-80.2; p=0.02) respectively, compared to those with MDR/XDR/Poly TB when adjusting for ART initiation. Among the HIV co-infected patients, no significant predictors of death could be found and this may be due to the small sample size failing to show any statistical significance.

When died and default outcomes were combined and analysed as unsuccessful outcomes (see Table 3.5), not initiated on ART had 7.6 times the hazards of unsuccessful outcome compared to those initiated on ART (aHR=7.6; 95% CI:4.1-14.1; p=0.0001) adjusting for DRTB diagnosis. Patients with confirmed Rifampicin mono-resistance diagnosis and those with Rifampicin resistance diagnosed by GXP only had 13 times the hazards of unsuccessful outcomes (aHR=12.5; 95% CI:2.9-53.7; p=0.001) and (aHR=12.6; 95% CI:2.9-52.7; p=0.001) respectively compared to those diagnosed with MDR/XDR/PolyTB when adjusting for ART initiation.

Table 3.4: Predictors of default among HIV co-infected patients with any RRTB at CMJAH between Jan 2010 and Jan 2014.

Variables		Unadjusted Hazard Ratio	P-value	95% Confidence Interval		Adjusted Hazard Ratio	P-value	95% Confidence Interval	
Gender	**Female**	Ref							
	Male	0.711	0.11	0.467	1.081				
Age category	**<40 years**	Ref							
	>=40 years	0.640	0.067	0.398	1.031				
DR-TB Diagnosis	**MDR/XDR/Poly-resistant TB**	Ref				Ref			
	RIF mono-resistant TB	15.53	0.01	2.128	113.289	10.847	0.023	1.398	84.147
	RIF resistant by GXP	18.19	0.0001	2.501	132.288	10.59	0.022	1.398	80.240
ART	No	Ref				Ref			

	Yes	0.344	0.0001	0.196	0.604	0.13	0.0001	0.059	0.288
CD4 count	<200	Ref							
	200-350	0.826	0.592	0.410	1.662				
	350-500	0.408	0.135	0.126	1.321				
	>500	0.579	0.452	0.139	2.404				

Table 3.5: Predictors of unsuccessful outcomes (death and default) among HIV co-infected patients with any RRTB at CMJAH between Jan 2010 and Jan 2014.

Predictors		**Univariate analysis**				**Multivariable analysis**			
		Unadjusted Hazard Ratio	**P-value**	**95% conf interval**		**Adjusted Hazard Ratio**	**P-value**	**95% conf interval**	
Gender	**Female**	Ref							
	Male	0.778	0.179	0.540	1.12161				
Age category	**<40 years**	Ref							
	>=40 years	0.767	0.196	0.514	1.14605				
ART	**Yes**	Ref				Ref			
	No	2.639	0.0001	1.598	4.359	7.586	0.0001	4.074	14.126
Diagnosis DR-TB	**MDR/XDR/Polyresist**	Ref				Ref			
	RIF mono resistance	9.236	0.002	2.237	38.1294	12.505	0.001	2.910	53.743
	RIF resistant on GXP	12.319	0.0001	3.004	50.5177	12.563	0.001	2.994	52.717
Weight category	**50-59 kg**	Ref							
	<50 kg	1.524	0.066	0.972	2.388				
	60-70 kg	1.007	0.98	0.572	1.77387				
	>70 kg	0.931	0.848	0.448	1.9341				

4 CHAPTER 4: DISCUSSION

4.1 Introduction:

In the study we investigated what the RRTB treatment outcomes were, in an ambulatory urban setting, what the predictors of the unsuccessful treatment outcomes were and the time to unsuccessful outcomes. We also investigated the difference in outcomes in HIV co-infected compared to HIV uninfected patients.

The study observed a very high percentage of new patients diagnosed who had no history of prior TB disease, highlighting a high primary resistance pattern occurring and showing that transmission of DRTB in the community setting is higher and may be underestimated. There were very few patients diagnosed with MDRTB and XDRTB (only one patient with XDRTB). This may be the reason why we could not demonstrate the association of more extensive drug resistant TB with unsuccessful treatment outcomes as previously reported in other studies. Literature had shown that the more the baseline resistance patterns detected for example if diagnosed with pre-XDR and XDRTB, these patients were more likely to have poor treatment outcomes.[34] Sputum GXP testing diagnosed more patients with DRTB compared to sputum smear testing alone, highlighting the importance of GXP testing in all suspected TB patients.[2]

4.2 DRTB Treatment outcomes

The results from this study showed an overall poor successful outcomes (5.1% cured and 14% completed treatment), a proportion smaller than ever reported in any other study where decentralization of DRTB care was implemented. [4, 24, 34, 36]. Many studies report only MDRTB treatment outcomes, whereas this study reported any RRTB outcomes, showing paucity of studies investigating any RRTB treatment outcomes. No studies reported on clinic-based ambulatory treatment outcomes but community-based and centralized hospital DRTB outcomes were reported. The rate of successful DRTB outcome in this study was also worse than that reported by the World Health Organization for SA in their 2017 report, with success rates of 54% and 27% for MDR/RRTB and XDRTB respectively. [33] Two meta-analysis comparing community-based and traditional hospitalization of DRTB patients have reported successful outcomes above 60%. [6, 32] The meta-analysis by Williams et al included 16 studies from different parts of the world with high TB burden and South African data was included in their analysis. [32] The difference in successful outcomes seen in this study and the studies mentioned that reported higher success rates, may be due to the difference in HIV/TB co-

infection rate. This study reported a very high HIV/TB co-infection rate compared to the low co-infection rates reported in many of these studies. A study that reported outcomes of DRTB in a high HIV/TB co-infection rate in SA context had lower rate of co-infection compared to this study's observation. Farley et al reported HIV/TB co-infection rate of 38%, much lower rate than observed in this study. [14] It was routine in this study for patients presenting with any form of TB to be offered HIV counselling and testing. This shows consistent adherence of treatment guidelines for patients presenting with either HIV or TB to check for the other disease as they often present together. In SA TB patients co-infected with HIV had better ART coverage compared to previous years, with 88% of patients on ART according to the 2017 WHO TB Report.[33] Integrated TB and HIV care services have shown to improve treatment outcomes in studies.[8, 9, 19]

Another study observed similar poor outcome results, they assessed similar ambulatory care DRTB treatment outcomes in a slum setting in India, which showed successful outcome rate of 22% in a similar population of HIV/TB co-infected patients. [36] Another study in SA with similar high HIV prevalence setting reported better success rate of 46% in MDRTB treatment outcomes. [14] In our study we observed a very low cure rate of 5.3%, and this low rate may be due to patients not able to produce sputum at the end of treatment to confirm cure or that collection of sputum did not occur for whatever reason and hence they were classified at the end of treatment as completed treatment outcome, this leading to an underestimation of cured patients. In a low-income setting in Peru, ambulatory community based therapy for MDRTB patients reported impressive cure rate of 83%. [24] The study associated the high success rate for these patients with inclusion of PZA and ETO in their treatment regimen. In this study we observed that there was a high proportion of patients in whom Rifampicin resistance diagnosed on GXPert was never confirmed. The high proportion of unconfirmed GXPert Rifampicin resistance may account for the poor outcomes seen, as this could have been poly-resistant TB or XDRTB patients who were treated as though they had RRTB, as there was no culture nor LPA confirmation done to ascertain proper diagnosis and classification of these patients and appropriate therapy for them.

The proportion of deaths observed in this study was slightly lower than that reported in a meta-analysis by Weiss et al which reported 13% deaths. [6] The observed deaths in our study was much lower than seen in two other studies with high HIV/TB co-infection rate, with death rates ranging from 17% to 25%. [14, 36, 45] Seung et al showed that mortality remained high in HIV/MDRTB co-infected patients in a study done in Lesotho in a community-based care

model. [47] Deaths remained similar to a study from a low income setting in Peru at 8%. [24] In another study with HIV/TB co-infection high burden setting in South Africa where community based treatment of DRTB was done, they reported better successful outcomes of 52% although the deaths were slightly higher than seen in our study at 13%. [4] Data has shown that the proportion of deaths was higher among TB patients who were co-infected with HIV than uninfected patients, although ART initiation improved survival in these co-infected population in a South African study. [8] The proportion of deaths observed in this study was much lower than that reported in a centralized care model (which also had high HIV/TB co-infection rate) seen at the referral centralized care model, which found death rate of 23% in a study reported by Umanah et al. [40] This difference may be due to the fact that the centralized care model had patients who were more sick warranting hospitalization, with presence of cavitatory lesions and other co-morbid conditions. We observed that there was no statistical difference in the proportion of those who died when stratified by HIV status in this study, this finding was contrary to findings in few studies showing poor survival of HIV co-infected patients. [4, 8, 14] The difference in deaths between HIV co-infected and those uninfected, observed in our study may be due to the high ART coverage. HIV/TB co-infection had no influence on early outcomes in patients with MDRTB in a study done in Botswana of patients receiving ambulatory DRTB care, the study showed no difference in proportion and time to sputum conversion when HIV positive were compared to HIV negative patients. [42] Padayatchi et al reported an 86% reduction in mortality when ART were initiated early in MDRTB patients on treatment. [13] The poor outcomes observed in our study with a high TB/HIV co-infection burden and a very high ART coverage of 83% conflicts with data reported by Abdool-Karim et al showing that integrated TB and HIV care improved survival of TB patients, although their patients had drug sensitive TB. [8]

Our study reported very high proportion of defaulting, with 28% of the patients having defaulted from therapy. A systematic review and meta-analysis by Weiss et al has shown a lower defaulter rate of 15%, from community-based treatment models. [6] Cox et al also reported slightly higher defaulter rate of 31% in a SA peri-urban community-based DRTB treatment setting with a high HIV burden. [4] They concluded that this may be due to poor tolerability and the long duration of DRTB treatment. [4] Severe adverse events were common within the first six months of therapy in a study by Schnippel et al [44] and this may increase the risk of defaulting and death within DRTB and HIV co-infected populations. Isaakidis et al reported similar high defaulter rate of 26% in an ambulatory care model in a HIV co-infected

population in a low socio-economic setting in India. [36] A study by Shean et al also reported a similar high defaulter rate (29%), although this study had very low HIV/TB co-infection rate of 9% and was not an ambulatory nor a community-based care model. [38]

We also observed a high proportion of transfer out, which is much higher than transfer out seen before in other studies in SA, ranging between 6% and 12%. [38, 40] Umanah et al study had very low transfer outs as this was a centralized DRTB site and a referral DRTB hospital, as patients will not have transferred elsewhere. [40] A meta-analysis by Johnston et al showed even lower transfer out rate of 2%. [35] In this study the high transfer rates occurred due to a high referral rate to a centralized DRTB treatment and referral centre, Sizwe Hospital. Whenever patients needed hospitalization for whatever reason, either when their sputum smear was positive or when they developed XDRTB or poly-resistance TB and needed to be referred and managed in a centralized facility, as the ambulatory care model in this study did not treat patients with pre-XDRTB, XDRTB or smear positive sputum after DRTB treatment was initiated.

No treatment failures were observed in this study, this was also reflected in other studies where DRTB treatment failure rates were low between 3% and 10%. [14, 32, 36, 40] Treatment failure was high in centralized compared to community treatment models as seen in a systematic review and meta-analysis by Williams et al. [32] The lack of failures in this study which showed less favourable outcomes may be due to early referral of patients to a centralized hospital whenever sputum conversion was not being achieved.

4.3 Time to unsuccessful outcomes (default and death)

Patients in this study defaulted and died very early in the study (within the first 3 to 4 months) after initiating DRTB treatment. Survival times for death outcome seen in this study are better compared to those seen in a study by Isaakidis et al with even a shorter survival time of 27 days in a HIV/TB co-infected population in slum Indian setting. [36] Early severe adverse events have been reported to occur within the first six months of DRTB therapy and associated with defaulting and death in patients receiving DRTB treatment in study reporting severe adverse events to DRTB treatment in a high HIV burden setting. [44] In patients with HIV co-infection, ARVs would further contribute due to overlapping of such severe adverse events to both the DRTB treatment and the ARVs. This might have contributed to the high defaulter rate in this study as majority of the patients were on ART as well, even though we did not seek to investigate when ARTs were initiated in conjunction with the DRTB drug initiation (before or after DRTB treatment), as Umanah et al investigated. A study by Gandhi et al, suggested that

deaths from MDRTB in HIV-infected patients were very high and usually occurred within the first 30 days after diagnosis. [46] Hoa et al has reported that half of the deaths occurred within the first 2 months after starting therapy, and the median time to default in China and Cambodia/Vietnam was 2 and 3 months respectively. [37] In another study done in Estonia, the median time to death was longer than we observed at 5 months. [28] Whereas a Russian study reported even shorter survival time with median time to death of just over a month. [43] Default happened throughout the study as reported by Moyo et al, contrary to our findings of very early default. [45] The reason for early default and death within the first 6 months after treatment initiation may be due to overlapping adverse events to both ARVs and anti-DRTB drugs, which were seen within the first 6 months of therapy in a study done in DRTB clinics with a high HIV burden. [44]

4.4 Predictors of unsuccessful outcomes (default and death)

The study did not have enough power to elucidate predictors of death due to small sample. Literature has described many predictors of death in patients with DRTB with or without HIV co-infection. A meta-analysis by Johnston et al reported being male a negative predictor of successful treatment outcomes. [35] Other predictors of death were low baseline weight <45kg and <60kg, which increased the hazards of death as seen in a South African study with high HIV prevalence. [14] This study failed to demonstrate low weight as a predictor of unsuccessful outcomes. We observed data that also showed low BMI was a negative predictor of death in a study by Mitnick et al. [24] In this study we couldn't analyse BMI as there was no recorded height for any of the patients in this data. Low baseline weight <45kg was also a negative predictor of failure outcome in the same study by Farley et al. [14] Age >35 years was also associated with a high hazard of death in another South African study by Moyo et al. [45] Being HIV positive was reported to have higher hazards of death, these patients had twice the odds of dying compared to the HIV uninfected patients in a study by Farley et al, although in another study in DRTB within a high HIV burden setting, infected patients had up to 86% less chances of death when started on ARVs. [14, 13] Studies reporting DRTB treatment outcomes in HIV co-infected patients have shown lower treatment success compared to studies with no HIV co-infection. [52-58] This emphasized what the guidelines advocate for, that when patients are co-infected with TB and HIV, initiation of ARVs for all these patients at the correct timing needed to improve their treatment outcomes. A meta-analysis by Johnston et al also found XDRTB diagnosis to be a predictor of poor outcomes. [35] This finding conflicts with our observation in this study which found RMRTB and RRTB on GXPert only (unconfirmed RRTB) to have

higher hazards of unsuccessful outcomes compared to MDRTB, XDRTB and poly-resistance TB diagnosis. The results also contradicted those reported by Brust et al, that showed that the more the baseline drug resistance and prior TB the higher the risk for treatment failure. [21] These results may have resulted due to the small sample and very low number of MDRTB, poly-resistant TB and XDRTB patients in the study, that may have led to failure to detect any association with unsuccessful outcome as previously reported.

The following predictors were associated with default in this study: RMRTB, Rifampicin diagnosed by GXP only and baseline weight loss. Weight loss has been found in other studies to be a risk factor of poor outcomes generally in DRTB patients. [14, 24] Weight loss has been reported as one of the key presenting symptoms of severe TB and HIV disease manifestation, and clinicians need to assess and correct any baseline weight loss with nutritional support to improve survival of these patients. A meta-analysis by Weiss et al failed to identify any predictors of successful outcomes. [6] The high defaulter rate within the first few months after commencing DRTB treatment may be associated with the injectable phase of intensive treatment and overlapping side effects from both anti-TB drugs and ARVs as seen in a study reporting adverse events in DRTB co-infected patients. [44] With a push towards shorter courses of treatments to improve adherence and completion of therapy, caution is still needed to address factors that impact negatively on early defaulting, as these factors may result in poor outcomes even with proposed shorter treatment regimen.

4.5 Predictors of unsuccessful outcomes among HIV co-infected patients

There was no statistical difference in proportions of those who died and defaulted when stratified by HIV status, except there was a significant difference in the proportion of the transfer out outcome, showing that a high proportion of HIV co-infected patients were transferred out (75%) compared no HIV uninfected in this study. This finding was contrary to those found in few studies showing a difference and poor survival of HIV co-infected patients. [8, 14, 46] Cox et al study reported earlier programmatic years and the poor survival of HIV co-infected patients may be due to low ARV coverage during that time period. [4] Among HIV positive patients in this study, being initiated on ART was a positive predictor of default. Initiated on ART had 90% less hazards of default than not initiated on ART. Data from other studies support this finding. Initiation of ART during anti-TB treatment in patients with MDR-TB was associated with 86% reduction in mortality in a SA study. [13] In two systematic reviews and meta-analysis in DRTB/HIV co-infected patients supported this finding that ARV

initiation improved MDRTB outcomes of these patients. [15, 35] Although in a study by Umanah et al, if HIV infected patients initiated ARVs before commencement of their DRTB treatment, the odds of mortality was higher than ARVs initiated after commencement of DRTB treatment. [41] This is surprising as ARVs should be protective, but they attributed their finding to poor adherence leading to virological failure among these patients then resulting in IRIS.

Among HIV positive patients, the positive predictors of default were being initiated on ART and age >40 years. Patients aged >40years had 40% less hazards of default compared to those aged <40years. This finding supports that in Moyo et al, where patients aged 15 - 25 years had higher hazards of defaulting in a community care model with high HIV co-infection setting. [45] There is more data supporting better adherence to treatment in older adults compared to younger adults who are HIV positive. [49 - 51] This may also support better adherence of these older patients to their anti-TB drugs when co-infected with HIV.

Other predictors of default were DRTB diagnosis of RMRTB and Rifampicin resistance on GXP only. This findings conflict with that reported from other studies that showed that if there was more extensive baseline resistance like pre-XDRTB and XDRTB, there were higher hazards of poor treatment outcomes than having mono-resistance patterns like RMRTB. [21, 34, 35] Again these results are due to small sample in the study and due to the very low number of MDRTB, poly-resistant TB and XDRTB patients, that may have led to our failure to detect any association with unsuccessful outcome as previously reported. The study was not powered to show predictors of death for HIV and TB co-infected patients in this study, due to the small sample size.

4.6 Potential study biases

4.6.1 Collection of exposure and outcome data

This study collected retrospective routine clinic data and have not measured all relevant factors. The date of DRTB diagnosis was not recorded in the data and hence could not analyse time from diagnosis to initiation of treatment for all patients. Other important factors like serial sputum culture results could have assisted in assessing sputum conversion times in the study. Height was not collected for 100% of the patients at baseline and hence could not calculate BMI. HB had a lot of missing data and where it was recorded, there were incorrect readings of the readings and could not be analysed as a predictor of poor outcomes. CXR findings were only recorded in a few patients and could not assess its impact on the outcomes.

Information bias was avoided by presenting blood results of TB, HIV, CD4 count from the referral clinics/hospital and where these laboratory tests were unavailable, they were collected to ascertain diagnosis to minimize misclassifying especially HIV status. DRTB diagnosis of Rifampicin Resistance on GXP without any confirmation by LPA/DST may have resulted in misclassification of DRTB diagnosis as these patients might have been either MDR/XDR/Poly-resistant TB had confirmatory tests (LPA/culture) been done.

Outcomes for the study were measured to avoid misclassification bias, as cured outcome was based on laboratory confirmation of consecutive negative cultures and DST, and all patients were followed up for a year after treatment was completed to ascertain successful outcomes. Tracing of patients who default any appointment date was strict and patients were only classified as defaulted after 2 consecutive months. Misclassification of outcome may have occurred if patients had died at home and the death couldn't be ascertained by contacting the family/relatives of patients by the clinic, then the patients would be misclassified as defaulted.

There was only one patient in the study diagnosed with XDRTB and few only diagnosed with poly-resistant TB, therefore these were merged together with MDRTB category, this may have introduced some biasness were only few patients in the study diagnosed with MDRTB and they XDRTB

4.6.2 Residual confounding and missing data of some of the exposure variables

Exposure variables were correctly stratified to limit possible confounding. Univariable analysis were done for unsuccessful outcomes, defaulted and died and included only those factors with a p-value<0.1 into the multivariable models in order to adjust for other factors to reduce residual confounding. Only factors with p-value<0.05 were considered as significant predictors of default, died and unsuccessful outcomes. The association found between the exposure variables and the outcomes was not due to chance.

This study collected retrospective routine clinic data and have not measured all relevant factors of interest. The date of DRTB diagnosis was not recorded in the data and hence could not analyse time from DRTB diagnosis to initiation of treatment for all patients. Other important factors like serial sputum culture results could have assisted in assessing sputum conversion times in the study. Height was not collected for all the patients at baseline and hence could not calculate BMI nor analyse the impact of BMI on our outcomes in this study. HB had a lot of missing data and where it was recorded, there were incorrect readings of the variable and could

not be analysed as a predictor of poor outcomes. CXR findings were only recorded in a few patients and could not assess its impact on the outcomes.

4.7 Study limitations

As this was a retrospective study, some of the observations in the data were missing for example data on co-morbidities, CD4 counts, VL, height, and weight. This may have affected the statistical power to detect such variables as significant predictors during the multivariable analyses. Failure to analyze VL for HIV positive patients and HB due to these variable data completely missing. The sample size was small and hence not powered enough to show an association between unsuccessful outcomes and the predictors. The small sample of extensive DRTB patients may have resulted in failure to show an association with unsuccessful outcome. The quality of data was not of a good standard.

The study lacked data for inpatient (hospitalised) treatment outcomes and also lacked the opportunity to treat patients within their communities in order to compare these models with the clinic based ambulatory treatment outcomes within this study. There was a lack of data on DRTB drug regimen initiated on individual patients to assess the impact of different regimens on outcomes. In earlier clinic years, before standardized DRTB guidelines were developed, clinicians would initiate individualized as opposed to standardized regimens, but this was not recorded to allow comparison between standardized and individualized therapy. Use of baseline variables for example CD4 count and weight may not give a true picture of association with the outcomes as these are time-varying variables and may improve with time. This may be the reason low baseline CD4 count could not show any association with poor outcomes in the study as these outcomes occur over a period of time.

4.8 Study strengths

The exposure variables were collected for this study before the outcome occurred and this ensured temporal relationship between the exposure variables and the outcomes. The study not only assessed MDRTB but any Rifampicin resistance including Rifampicin mono-resistance, poly-resistant TB, pre- and XDRTB and MDRTB, and this included patients diagnosed by GXP alone and not confirmed by either LPA or DST.

4.9 Generalizability

This study may not be generalizable to other settings due to it being in an urban highly mobile population setting in the city of Johannesburg, and may not be generalizable in rural or peri-urban settings. The DRTB/HIV co-infection rate is the study is very high and may not be generalizable in low HIV prevalence settings, and the results of this study must be interpreted with caution in other settings. The ART coverage of this study was also very high and in settings where ART coverage is still low, the results must be interpreted with caution.

5 CHAPTER 5: CONCLUSION & RECOMMENDATIONS

5.1 Conclusion

In conclusion, this study in an ambulatory urban setting showed no better successful outcomes with a high defaulter rate when compared to rural or peri-urban community-based care models and other ambulatory care models for DRTB patients in a high HIV burden clinic. There were comparable deaths and no treatment failures seen in the study. Death and defaults happened early within the first 6 months which fell within the intensive phase (injectable phase) of DRTB therapy, further supporting the need for alternative short course non-injectable treatments. ART initiation among the DRTB and HIV co-infected patients reduced the hazards for unsuccessful outcomes (both death and default). Median survival time for unsuccessful outcomes were very short falling within the intensive phase of DRTB therapy. Predictors of default were RMRTB, Rifampicin diagnosed by GXP only and baseline weight loss. Positive GXP results showing Rifampicin resistance need to be There were no predictors of mortality found in this study. For a subgroup of HIV co-infected patients, being initiated on ART was associated with 90% less hazards of defaulting. Age category >40 years had less hazards of defaulting among HIV co-infected patients and reduced the hazards of default by 60%. Confirmed RMR-TB and unconfirmed Rifampicin-resistance diagnosed on GXP were also predictors of default among HIV co-infected patients. There was no difference found in proportions of successful and unsuccessful outcomes between HIV co-infected and HIV negative patients.

5.2 Recommendations

In summary, the high defaulter rate within the first few months after commencing DRTB treatment impacts negatively on the control of DRTB, hence efforts to improve defaulting from care are needed. Addressing factors associated with defaulting is crucial in DRTB clinics to curb transmission of DRTB in the community. All Rifampicin resistant results on GXP need immediate confirmation by LPA and culture/DST, to avoid treating DRTB patients inappropriately. Clinicians need to follow DRTB management guidelines for diagnosis and treatment, as these patients may be XDRTB or Poly-resistant TB who are treated as though they were RMRTB or MDRTB cases. Integrating DRTB and HIV management services has positively impacted on the outcomes of DRTB in HIV co-infected patients, a programme that needs to be broadly implemented and supported by both government and non-governmental institutions. ART initiation for all DRTB patients is needed at appropriate timing to improve

survival of HIV co-infected patients. Tracing of transfer out to determine final outcomes is needed, to avoid underestimation of successful outcomes in national TB programmes. The study confirms that starting ART in DRTB and HIV co-infected patients will result in better retention within the health care system and in turn improve the treatment outcomes for patients DRTB and HIV co-infected patients. The early deaths and defaults highlight the importance of close monitoring of these patients during the intensive phase of therapy, intensifying adverse event monitoring and reporting by both patients and clinicians. This echoes the need for short-course treatment regimen, without injectable treatments. With a push towards short course treatment regimen to improve adherence and treatment outcomes, caution is still needed to address factors that impact negatively on early defaulting and deaths as this will impact negatively on any of these short treatment regimen.

5.3 Potential areas of further research

Explore further why clinicians were not confirming positive sputum GXPert results and seek to understand their knowledge gaps in treating DRTB even when DRTB management guidelines were available. A more powered study with a larger sample size should be conducted to further explore and understand why patients defaulted early during the treatment journey. Newer treatment regimens aim to decrease early defaulting in these patients, lack of understanding of predictors of early default may see even these new short duration treatments not being successful as patients dropped out of care as early as 1 to 6 months after DRTB treatment was started.

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7 Appendices:

Appendix 1: Plagiarism declaration form

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Norah Maitisa (Student number: 297119) am a student registered for the degree of MSc Epidemiology in the academic year 2018

I hereby declare the following:

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

Signature: [signature] Date: 06/06/2018

26/04/2015
1

Appendix 2: Bivariate Cox regression analysis of predictors of unsuccessful DRTB treatment outcomes (death and default) at CMJAH 2010 - 2014

Independent variables		Hazard Ratio	P-value	95% CI	
Gender	**Female**	1	(Base)		
	Male	0.778	0.179	0.540	1.122
Age category	**<40 years**	1 (base)			
	>=40 years	0.767	0.196	0.514	1.146
HIV status	**Negative**	1	(base)		
	Positive	1.095	0.752	0.625	1.916
Diagnosis patient category	**New**	1 (base)			
	reRx_reg1	1.280	0.234	0.852	1.922
	reRx_reg2	1.413	0.559	0.444	4.494
ART	**No**	2.639	0	1.598	4.359
	Yes	1 (base)			
Bactrim prophylaxis	**No**		1 (base)		
	Yes	1.414	0.206	0.827	2.417
Refering facility	**PHC**	1	(base)		
	Private facility	0.474	0.459	0.066	3.421
	CMJAH wards/OPD	1.123	0.741	0.565	2.230
	Other hospital	1.367	0.425	0.634	2.947
Employment	**Employed**	1 (base)			
	Unemployed	1.641	0.167	0.813	3.309
	Unknown	1.516	0.199	0.804	2.858
Education	**Education**	1	(base)		
	No Education	1.199	0.565	0.645	2.228

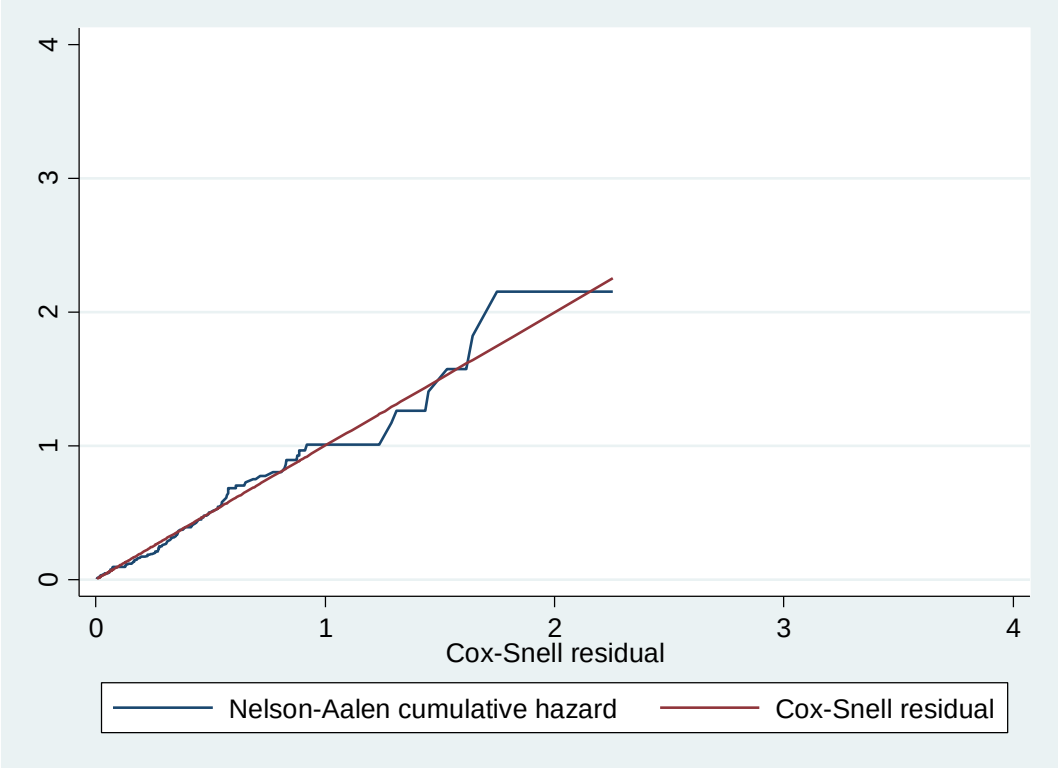
Nationality	**South African**	1	(base)		
	Non-SA	1.661	0.388	0.525	5.255
cd4_grp	**<200**	1	(base)		
	200-350	0.753	0.361	0.410	1.383
	350-500	0.470	0.106	0.188	1.174
	>500	0.416	0.224	0.101	1.709
diagnosis DR-TB	**MDR/XDR/Polyresis.**	1	(base)		
	RIF mono-res..	9.236	0.002	2.237	38.129
	RIF resistan..	12.319	0	3.004	50.518
Weight category	**<50 kg**	1.524	0.066	0.972	2.388
	50-59 kg	1 (base)			
	60-70 kg	1.007	0.98	0.572	1.774
	>70 kg	0.931	0.848	0.448	1.934
weight		0.981	0.041	0.963	0.999

Appendix 3: Test of proportional assumption

	Test of proportional-hazards assumption table			
Factors	rho	chi2	df	P-value
Gender	0.04654	0.2	1	0.658
Age category	-0.02517	0.06	1	0.811
ART	-0.13295	1.62	1	0.2025
Diagnosis DRTB	-0.01587	0.02	1	0.8996
Weight category	0.0995	0.97	1	0.3247
global test		3.08	5	0.6881

No violation of the proportional hazard assumption was observed

Appendix 4: Goodness of fit for the final model



The hazard function follows a 45degree line; we can assume the model fit the data well

Appendix 5: Written permission from the CMJAH on conducting research

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries: Ms. Lefentse Mapa
Office of the Clinical Executiv
Tel: (011)488-3710
Fax: (011)488-3947
04 December 2014

Dr. Norah Maitisa
Wits Reproductive Health & HIV Institute
Faculty of Health Sciences - University of the Witwatersrand

Dear Dr. Maitisa

RE: "Drug resistant tuberculosis treatment outcomes at an urban ambulatory TB unit in th City of Johannesburg."

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic hospital will not in any way incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the Head of Department and Unit Manager or Sister in Charge to agree on the dates a time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 5/12/2014

Approved / not approved

Ms. G. Bogosi
Chief Executive Officer
DATE: 5/12/2014

Appendix 6: Human Research Ethics Committee Clearance certificate

R14/49 Dr Norah Maitisa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M141033

NAME: (Principal Investigator)	Dr Norah Maitisa
DEPARTMENT:	Public Health Wits Reproductive Health and HIV Institute
PROJECT TITLE:	Drug Resistant Tuberculosis Treatment Outcomes at an Urban ambulatory Tuberculosis Unit in the City of Johannesburg
DATE CONSIDERED:	31/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Charles Chasela
APPROVED BY:	Professor C Feldman, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/12/2014

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

DECLARATION OF INVESTIGATORS

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

Principal Investigator Signature Date 2014/12/20

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES