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Effects of timing of the antiretroviral therapy initiation on multidrug-resistant tuberculosis outcomes in HIV co-infected patients in Sizwe tropical disease hospital, Johannesburg, South Africa, 2007-2010

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EFFECTS OF TIMING OF ANTIRETROVIRAL THERAPY INITIATION ON MULTIDRUG-RESISTANT TUBERCULOSIS OUTCOMES IN HIV CO-INFECTED PATIENTS IN SIZWE TROPICAL DISEASE HOSPITAL, JOHANNESBURG, SOUTH AFRICA, 2007-2010.



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

Johannesburg, October 2014

DECLARATION

I, Dr Teye Aniefiok Umanah, declare that this research report is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology (Infectious Disease Epidemiology), in the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination in any other University.

Signature:  Date: 23rd October, 2014

DEDICATION

This work is dedicated to my husband Dr Attai Gregory Ikafia for his sponsorship and encouragement during the learning process of the entire programme and my first son Ifiokobong Attai Ikafia who was three months old when I started this programme.

ABSTRACT

Background

Multidrug-resistant tuberculosis (MDR-TB) is a threat to global tuberculosis (TB) control. Its management in human immunodeficiency virus (HIV) co-infected patients has been a challenging experience. There is however paucity of data on the effects of antiretroviral treatment (ART) before or after starting MDR-TB treatment. **Therefore the objectives of this study were to** describe the clinical characteristics and outcomes of MDR-TB treatment; and determine the predictors of mortality, cure and failure in HIV-TB co-infected patients who were started on ART before and after commencement of MDR-TB treatment.

Methods

A retrospective review of medical records of 1,200 MDR-TB HIV co-infected adults from Sizwe Tropical Disease Hospital from 2007 to 2010. The relationship between outcomes of MDR-TB treatment and independent covariates including receiving ART before or after commencement of MDR-TB treatment were assessed using chi-square test or Fisher's exact test, and the t-test or the Mann-Whitney test where appropriate. Multivariable logistic and Poisson regression models were used to determine predictors of mortality, cure, and failure.

Results

Outcomes did not differ significantly by timing of ART initiation except for mortality which was higher among patients who started ART before (21.8% vs. 15.4%) MDR-TB treatment initiation ($p = 0.013$). Factors significantly associated with mortality included: the use of ART before commencement of MDR-TB treatment (OR: 1.76; [1.07-2.91]), being severely underweight (OR: 3.46; [1.77-6.77]) and underweight (OR: 2.31; [1.28-4.15]), cavitary lesions on baseline chest x-rays (OR: 1.83; [1.13-2.96]), presence of other opportunistic infections (OR: 1.85; [1.13-3.00]) and the presence of other co-morbidities (OR: 2.51; [1.34-

4.68]). For predictors of cure, there was a significant interaction term between timing of ART initiation and gender (p = 0.002).

Factors that positively predicted cure were male patients on ART prior to commencement of MDR-TB treatment (OR: 2.97; [1.47-5.99]), age ≥46 years (OR: 1.65; [1.05-2.59]), and CD4 counts between "150-349" (OR: 1.85; [1.26-2.72]) and" ≥350" (OR: 1.76; [1.02-3.04]) cells/mm³. Negative predictors of cure included: the presence of cavitary lesions on baseline chest x-rays (OR: 0.55; [0.39-0.79]), and modified individualised regimen at baseline (OR: 0.62; [0.42-0.92]). Risk factors for failure included: severe anaemia (IRR: 3.94; [1.20-12.89]) and modified individualised regimen at baseline (IRR: 2.25; [1.02-4.95]).

Discussion and Conclusions

This study is unique as it provides new information while also reinforcing old knowledge to clinicians and public health practitioners for the identification of TB populations at higher risk of death, treatment failure and decreased cure. High mortality among patients who were already on ART before commencement of MDR-TB treatment raise concerns about general ART adherence and monitoring at different HIV clinics across Gauteng Province.

Clinicians should not undervalue the role of adherence to ART treatment in patients on ART before commencement of MDR-TB treatment. Management of existing adverse events, opportunistic infections and co-morbidities in these patients are important to maximise the protective benefits of being on ART before commencement of MDR-TB treatment. There is need to intensify intervention programmes targeted at increasing adherence and drug monitoring among HIV co-infected MDR-TB patients.

Key words: *Multidrug Resistant Tuberculosis (MDR-TB), Human Immune-deficiency virus, Antiretroviral Treatment, 'HIV co-infected MDR-TB'.*

ACKNOWLEDGEMENTS

My sincere gratitude goes to my supervisors Prof Peter Nyasulu of Monash South Africa and Mr Jabulani Ncayiyana of the University of the Witwatersrand and University of North Carolina for their selfless and tireless supervision, and encouragement towards the successful completion of this report. I am thankful to all the lecturers of the Wits School of Public health for their tutoring and guidance during the course work. Thanks must also go to Dr Eustasius Musenge who gave invaluable advice during the statistical analysis of this report. Mrs Angeline Zwane also deserves mention for her warm smiles and efficiency as the Course Administrator. To all my course-mates, especially Caroline Govathson and Charity Vhrumuku; thank you for your friendship and making the masters programme year worthwhile.

I am most grateful to Dr Rianna Louw, the CEO of Sizwe Tropical Disease Hospital, Johannesburg for her warm reception and granting me permission to review records from the hospital. I also want to thank Dr Xavier Padanilam the Chief Medical Officer of Sizwe Hospital for his guidance and contributions during the data collection and while writing up this research. To Sister Tshilidzi Emelda Ramatshila and all the staff of Gateway clinic, thank you for such a show of love and support during the data collection process. My appreciation goes to Mr Magaga Mokhine the Chief clerk of Sizwe records unit for mobilising and co-ordinating the entire clerical staff to help in pulling out records daily for me to review. I learnt humility again from you. To Mr Joseph Mosenohi, Mrs Constance, Mrs Onicca, Mrs Magdalene and other OPD clerical staff, nurses and cleaners who were all so supportive while collecting the data; the medical records review would not have been possible without you all.

I do remember Dr Linda Erasmus who helped me get in contact with Sizwe Hospital and Ananta Naidoo for her helpful inputs during the protocol development stage.

Special thanks go to my family members for their prayers and encouragement, and to my husband for his love and immense support. I cannot fail to acknowledge my son, Ifiokobong whom I repeatedly left alone in the care of nannies while pursuing this course and my unborn son “Abasi-ono” whom I conceived while collecting data and writing up this research.

Finally, an overwhelming recognition to God Almighty in whom I live, move and have my very being and by whose grace I can do all things.

CONTENTS

DECLARATION.....i
DEDICATION.....ii
ABSTRACT..... iii
ACKNOWLEDGEMENTS v
LIST OF FIGURES x
LIST OF TABLES xi
ABBREVIATIONS.....xii
CHAPTER 1: INTRODUCTION.....1
1.1 Background.....1
1.2 Statement of the problem.....2
1.3 Justification.....4
1.4 Research question 4
1.5 Literature review.....5
1.5.1 General effect of the HIV epidemic on treatment outcomes of TB- pre and post TB-ART integration programmes.....5
1.5.2 MDR-TB outcomes, HIV co-infection and ART.....5
1.5.3 Predictors of cure, failure and mortality.....8
1.5.4 Outcomes in MDR-TB/HIV co-infected patients based on the timing of initiation of ART.....9
1.6 Study aim 10
1.6.1 Specific objectives.....10
CHAPTER 2: METHODS 11
2.1 Study design.....11
2.2 Study setting.....11
2.3 Study population 12
2.4 Study sample.....12
2.4.1 Inclusion criteria:.....12
2.4.2 Exclusion criteria: 12
2.5 Data sources and measurement.....13
2.6 Data collection 15
2.7 Outcome variable 15
2.8 Exposure variables.....15
2.9 Definition of study variables.....15

2.9.1 Outcome variables 15
2.9.2 Exposure variables 17
2.9.2.1 Socio-demographic variables 17
2.9.2.2 Clinical information 17
2.10.0 Data management 18
2.11.0 Data analysis 19
2.11.1 Descriptive and inferential statistics 19
2.11.2 Assessment of effect modification and confounding 20
2.11.3 Univariable and multivariable analyses 20
2.11.4 Model diagnostics 22
2.12.0 Ethical considerations 22
CHAPTER 3: RESULTS 23
3.1 Baseline characteristics 23
3.2 Inferential statistics 30
3.3 Outcomes of MDR-TB by ART treatment groups 33
3.4 Assessment of effect modification and confounding 34
3.4.1 Mortality 34
3.4.2 Cure 34
3.4.3 Failure 34
3.5 Predictors of mortality 34
3.5.1 Univariable logistic regression models 34
3.5.1.1 Socio-demographic factors 35
3.5.1.2 Clinical factors 35
3.5.2 Multivariable logistic model 36
3.5.2.1 Clinical factors 36
3.6 Predictors of cure 39
3.6.1 Univariable analyses 39
3.6.1.1 Socio-demographic factors 39
3.6.1.2 Clinical factors 39
3.6.2 Multivariable logistic model 40
3.6.2.1 Socio-demographic/clinical factors 40
3.7 Predictors of failure 44
3.7.1 Univariable Poisson regression analysis 44
3.7.1.1 Clinical factor 44
3.7.2 Multivariable Poisson analysis 44

3.7.2.1 Clinical factors....44
CHAPTER 4: DISCUSSION....47
4.1 Introduction....47
4.2 Systematic overview of the study findings....48
4.2.1 Predictors of mortality....48
4.2.2 Predictors of cure....51
4.2.3 Predictors of failure....53
4.3 Potential study biases....54
4.3.1 Collection of exposure and outcome data....54
4.3.2 Residual confounding and missing data of some of the exposure variables....55
4.4 Study limitations....56
4.5 Study strengths....57
4.6 Generalizability....58
CHAPTER 5: CONCLUSION AND RECOMMENDATIONS....59
5.1 Conclusion....59
5.2 Recommendations....59
5.3 Suggestions for further studies....61
REFERENCES....62
APPENDICES/ ANNEXURES....71

LIST OF FIGURES

Figure 3.1: Exclusion and inclusion criteria flowchart of the cohort.

Figure 3.2: Outcomes of MDR-TB treatment in HIV co-infected adults at Sizwe Tropical Disease Hospital Johannesburg from 1st January, 2007 to 31st December, 2010.

Figure 3.3: ART status of patients on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Figure 3.4: Duration on ART treatment in MDR-TB HIV co-infected adults at Sizwe Tropical Disease Hospital, Johannesburg.

Figure 3.5: Tab-plots of MDR-TB treatment outcomes by timing of ART initiation showing frequencies and proportion of patients in each outcome category.

LIST OF TABLES

Table 3.1.1: Baseline demographic characteristics of HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Table 3.1.2: Baseline clinical characteristics of HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Table 3.2.1: Bivariate analysis of demographic characteristics of MDR-TB HIV co-infected adults based on exposure to ART before or after commencement of MDR-TB treatment.

Table 3.2.2: Bivariate analysis of clinical characteristics of MDR-TB HIV co-infected adults based on exposure to ART before or after commencement of MDR-TB treatment.

Table 3.2.3: Bivariate analysis of outcomes of MDR-TB in HIV co-infected adults based on commencement of ART before or after initiation of MDR-TB treatment.

Table 3.3: Predictors of mortality in HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Table 3.4: Predictors of cure in HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Table 3.5: Predictors of failure in HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Table 3.6.1: Predicted log-odds of the interaction term between timing of ART initiation and gender for cure model.

Table 3.6.2: Predicted probabilities of the interaction term between timing of ART initiation and gender for cure model.

ABBREVIATIONS

AIC - Akaike International Criterion

AIDS - Acquired Immunodeficiency Syndrome

AM - Amikacin

ART - Antiretroviral Therapy

ARVs - Antiretroviral Drugs

BMI - Body Mass Index

CD4 - Cluster of Differentiation 4

CFR - Case Fatality Rate

CM - Capreomycin

CMV - Cytomegalovirus

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

HAART - Highly Active Antiretroviral Therapy

HIV - Human Immunodeficiency Virus

HSV - Herpes Simplex Virus

IP - Intensive Phase

IQR - Interquartile Range

IRIS - Immune Inflammatory Response Syndrome

IRR - Incidence Rate Ratio

KM - Kanamycin

KS - Kaposi Sarcoma

LPA - Line Probe Assay

MDR-TB - Multidrug Resistant Tuberculosis

MFX - Moxifloxacin

MGIT - Mycobacterial Growth Indicator Tube

MTB - Mycobacterial Tuberculosis

NHLS - National Health Service Laboratory

OR - Odds Ratio

PCP - Pneumocystis Jirovecii Pneumonia

PTB - Pulmonary Tuberculosis

PZA - Pyrazinamide

RLS - Resource Limited Settings

SD - Standard Deviation

SSA - Sub-Saharan Africa

ST - Still on Treatment

TB - Tuberculosis

TC - Treatment Completed

TD - Treatment Defaulted

TDR - Teridizone

TF - Treatment Failure

TO - Transfer Out

VIF - Variance Inflation Factor

WHO - World Health Organisation

CHAPTER 1: INTRODUCTION

This chapter gives an overview of the burden of tuberculosis (TB) and multidrug-resistant TB (MDR-TB), as well as the rationale for the study and ends with an explicit review of relevant literature on the subject.

1.1 Background

Globally, there were an estimated 8.6 million incident cases of TB in 2012 of which 13% were co-infected with Human immune-deficiency virus (HIV) (1). Out of these, 1.3 million TB-related deaths were recorded with about 320,000 deaths in HIV co-infected individuals and 940,000 among HIV-negative TB patients (1). About 75% of the TB cases among HIV-infected patients occurred in Africa. South Africa and Swaziland had the highest TB incidence rate of about 1 case per 100 persons each year (1).

TB is primarily a disease of the lungs caused by an organism called Mycobacterium TB (MTB) and could present as a latent or active disease. It is the leading cause of death from infectious diseases especially amongst people living with HIV and Acquired Immunodeficiency Syndrome (AIDS) (1, 2). The spread of the bacilli to other parts of the body including lymph nodes, gastro-intestinal tract, viscera, kidneys, bones and the central nervous system results in extra pulmonary TB (EPTB), which can be treated with the conventional first line anti-tuberculous agents.

About 450,000 incident MDR-TB cases were diagnosed globally among pulmonary TB (PTB) patients in 2012 (1), which is an increase compared to 2011 (320,000 cases) (3). South Africa has the world's third highest TB and drug resistant TB (DR-TB) burden (1). DR-TB develops as a complication of poorly treated TB and as a consequence of deficiencies in TB control programmes (4-6). From the 2013 World Health Organisation (WHO) global estimate

of TB cases, about 3.6% of the new cases and 20.2% of previously treated patients have been estimated to have MDR-TB (1).

MDR-TB is defined as TB caused by MTB resistant in vitro to the effects of Isoniazid (INH) and Rifampicin (R), with or without resistance to any other drug. It could arise also from primary infection. Extensively drug resistant TB (XDR-TB) is defined as MDR-TB plus the resistance to any of the fluoroquinolones and any one of the second-line anti-tuberculous injectable drugs (Amikacin (AM), Kanamycin (KM) and Capreomycin (CM)). Treatment of DR-TB is expensive and takes a longer duration of at least 18-24 months. The most common treatment regimen for MDR-TB utilises five drugs namely KM/AM, Moxifloxacin (MFX), Ethionamide (ETO), Terizidone (TDR), Ethambutol (EMB) and Pyrazinamide (PZA) for at least 6 months during the intensive phase (IP), followed by at least 18 months of MFX/ETO/PZA/TDR after culture conversion for the continuation phase (CP) (7). Treatment is done first on an in-patient basis (not applicable to decentralised treatment centres) for at least 6 months (IP) while monitoring for sputum culture conversion until after conversion, and subsequently CP.

1.2 Statement of the problem

MDR-TB poses a threat to global TB control programmes (8), and this is aggravated in resource limited and low-income countries due to inadequate availability of prompt diagnostic and treatment measures (9). The incidence of MDR-TB has been shown to be rising especially among HIV positive patients in Sub-Saharan Africa (SSA), even though the incidence of TB has been noticed to be declining (1). The co-infection of MDR-TB and HIV has been aptly described by Wells et al. as the "Perfect storm" (10). About 170,000 of the 1.3 million TB deaths globally in 2012 were due to MDR-TB (1).

South Africa is included as one of the countries by the WHO to have over 80 percent of notified estimated MDR-TB cases worldwide with about 10,085 notified cases in 2012 (1). The 2001/2002 TB drug-resistant survey conducted by the Medical Research Council of South Africa revealed that 1.6% of patients with newly diagnosed TB and 6.6% of patients previously treated for TB had MDR-TB isolated from their sputum (11). This data may not be correct anymore as results of the on-going drug-resistant survey is being awaited. In South Africa the MDR- and XDR-TB epidemic have mainly been driven by the HIV epidemic and inadequate airborne infection control (12). It has been reported that over 80 percent of MDR- and XDR-TB patients in South Africa are HIV positive (13). The rapid spread of MDR-TB among HIV-positive patients is due to the impaired ability of the immune system to contain the MDR-TB bacilli in these patients as this applies also to the normal TB bacilli (14). The probability of progression from latent TB to active disease is 20-30 times higher in HIV infected individuals compared to those uninfected (15).

Diagnosis and treatment of MDR-TB has been quite a challenging venture around the globe especially in the resource limited settings (RLS). This is even more difficult among HIV-infected individuals as the classical symptoms of PTB may not be as pronounced as in HIV negative patients. Also HIV positive patients are sometimes smear negative, hence presentations of TB amongst these patients may be over-looked and attributed to the HIV infection. Further difficulties in early diagnosis can be ascribed to delays in results of drug susceptibility testing (the gold standard for diagnosis of MDR-TB) which is sometimes not feasible at baseline for all patients. The adverse events from lifelong treatment of HIV with antiretroviral therapy (ART) coupled with side effects from MDR-TB drugs makes the management and outcomes of MDR-TB in co-infected patients a nightmare for most physicians.

1.3 Justification

Studies have compared treatment outcomes of MDR-TB with documentations of fatal and poor outcomes in co-infected patients prior to the scaling up of ART (16-18). Studies conducted after the roll-out of ART reveal better outcomes for MDR-TB (19-21); however, these studies were done to ascertain outcomes of MDR-TB for both HIV infected and uninfected individuals with the number of enrolled HIV-positive patients ranging between 40 to less than 300 not considering the timing of ART initiation. Research work carried out on timing of ART initiation in patients with pan susceptible TB used ARV-naïve TB patients (22), without looking at the effect of ART initiation before the start of TB treatment.

There is paucity of studies conducted in SSA on the effect of timing of ART initiation before or after commencement of MDR-TB treatment on MDR-TB outcomes in HIV positive patients. Data on this is highly needed in order to help evaluate the efficiencies/deficiencies of MDR-TB treatment and ART programmes. Therefore it is essential to ascertain the role timing of introduction of ART plays in the management of patients with MDR-TB and HIV co-infection. Such findings would be used to guide policy change so as to improve MDR-TB treatment among HIV co-infected patients in South Africa.

1.4 Research question

What are the effects of timing of ART initiation on the treatment outcomes of MDR-TB in TB-HIV co-infected patients in South Africa?

1.5 Literature review

1.5.1 General effect of the HIV epidemic on treatment outcomes of TB- pre and post TB-ART integration programmes

TB treatment in HIV co-infected patients has evolved over the years. A lot of controversies exist due to the complications associated with the treatment. High case fatality rates (CFR) were documented despite effectiveness of anti-tuberculous drug treatment (23, 24). Mukadi YD et al. demonstrated higher CFR in smear negative and extra-pulmonary patients than in smear positive cases (23). They attributed this increased mortality to HIV-related diseases and not necessarily TB and to the increased demands of the HIV epidemic on the general healthcare services and delivery in-terms of facility/material resources and man-power (23). It must be noted, however, that these studies were done before the integration of HIV-TB treatment programmes.

Following the integration of TB-HIV treatment, problems evolved around the ideal initiation time of ART during TB treatment. This was due to the increased rates of Immune Reconstitution and Inflammatory Syndrome (IRIS) in HIV co-infected patients who had very low CD4 cell count. IRIS has been shown to be associated with early initiation of ART and could increase mortality in these patients (25-27), but Karim SS et al. had little or no deaths attributable to IRIS. This could also be due to the fact that mortality in their study was characterised as all cause (28). There is mounting evidence of improved treatment outcomes of TB with early ART initiation, notable among them is the clinical trial done by Karim SS et al. (28, 29).

1.5.2 MDR-TB outcomes, HIV co-infection and ART

Systematic reviews and meta-analysis results based on data from different continents and over 21 countries have revealed a relatively low successful MDR-TB treatment outcome of about 62-64% (30, 31). For these studies, successful treatment was defined as a combination

of cure and "treatment completed" based on the WHO classification of treatment outcomes. Both studies also had similar levels of outcomes in terms of failure (6-8%), default (12-13%), died (11%) and transferred out (2%) (30, 31). However, the study by Orenstein EW et al. combined transferred out and defaulted treatment as one outcome. The review by Orenstein EW et al. included only two of the 22 high TB burden countries and had no study from SSA, but Johnston JC et al. included one study from SSA where the incidence of MDR-TB and the prevalence of HIV are different from the rest of the included populations [this was a randomised control trial conducted in South Africa between 1992-2002; a study by Shean KP et al. (32)] (31). These reviews also had inconsistently reported HIV status from the pooled studies used.

A recent large individual patient data meta-analysis consisting of 9153 patients (33) documented very low proportion of treatment success which was slightly more than half of the patient population (54%) compared to other treatment outcomes (33). This study utilised data from three systematic reviews (30, 31, 34). The proportion of patients that died in the study was 15% and these were mainly older HIV positive patients. All of the aforementioned studies did lack data on the use of antiretroviral drugs.

In SSA, several studies have compared treatment outcomes of MDR-TB, in terms of cure, completed treatment, failure, default, and mortality between HIV co-infected patients and HIV negative patients, with documentations of poor and sobering outcomes in co-infected patients prior to the scaling up of ART (16-18). Data from this region especially from studies conducted in South Africa revealed much lower and poorer treatment success rates of about 43-46% (16-18), higher and earlier mortality rates of over 23% especially among HIV co-infected patients (16), higher default and treatment failure using a standardized treatment regimen when compared to the meta-analyses (30, 31) that used more studies with individualised treatment regimen than the standardised regimen.

Following the roll out of ART in SSA, there have been favourable treatment outcomes of MDR-TB among HIV co-infected patients with comparable and no statistically significant difference in the outcomes between negative and positive patients (19-21, 35). In a South African study by Brust JC et al., overall treatment success has been as high as 77% with the proportion of patients who died estimated to be as low as 6% and better retention in care with a minimal default rate of about 5% (19). The improved outcome in this study was attributed to the decentralised integrated, home-based MDR-TB/HIV treatment programmes (19). Similar results in terms of higher proportion of culture conversion were reported by Loveday M et al., using the same treatment model compared with centralised care (35). In this study, this difference was attributed to the shorter median time to MDR-TB treatment initiation and tight follow-up scheme adopted by the decentralised programme (35). However, there was no statistically significant difference in the probability of survival in patients using both models (35). Similar but lower proportions of default and treatment failure have also been noted in studies conducted in other parts of Southern Africa (20).

A study conducted in Lesotho by Satti H et al. with 134 MDR-TB patients out of which 94 (70%) were co-infected with HIV showed no difference in outcomes in terms of the proportion of deaths among the HIV/MDR-TB co-infected adults based on the timing of ART initiation, compared with patients not on ART (20). Nevertheless, it was noticed that the median survival time for those who were not started on ART after MDR-TB treatment initiation was shorter compared with those who commenced ART prior to or during MDR-TB treatment (80 vs. 138 days, $p = 0.065$); although patients who started ART after initiating MDR-TB treatment did so within a median duration of 16 days (20). Failure of achieving statistical significance in this study may have been due to the limited sample power. A common ground for these studies was comparison between HIV positive and negative patients. Only a few studies have reported outcomes of MDR-TB with concomitant ART

treatment in a high HIV prevalence setting from a cohort of HIV co-infected patients (36-38). This appears to be the first retrospective medical record review ascertaining treatment outcomes involving such a large cohort of only HIV positive MDR-TB patients.

1.5.3 Predictors of cure, failure and mortality

There are several factors that may predict poor outcomes of MDR-TB in general and more so among HIV co-infected patients. These are important because intervention can be modified based on these factors to improve treatment outcomes. Factors associated with poor treatment outcomes include male gender, smear positivity during diagnosis, low BMI, alcohol abuse, fluoroquinolones resistance, presence of XDR strains (31, 33, 39), and CD4 count <200 cells/mm³ (40); while individualised treatment regimen compared with standardised treatment regimen (30), history of no previous treatment and surgical intervention (30), have been associated with successful treatment outcomes. The majority of studies on outcomes of MDR-TB report cure and treatment completed as 'successful treatment'; but this study reports each outcome as a mutually exclusive entity since technically, the one does not denote the other.

Predictors of mortality and treatment failure include weight less than 60 kg (16), low/severely low body mass index (BMI) (16, 20, 31, 36, 41, 42), history of working in South Africa (20), and relapsed TB (43). Severe chest radiographic findings like cavitation have been associated with longer time to sputum conversion hence poorer outcomes like mortality and failure (43-45); however, some studies found no association between cavitary lesions and poorer outcomes (31, 46). Low baseline weight is documented to result in a 3-fold increase in the hazard of mortality compared with normal baseline weight (36). The presence of other co-morbidities has also been identified as a risk factor for mortality (47) in a study conducted in the United Kingdom. By examining the varying effects of ART on mortality, receiving ART has been shown to significantly lower mortality compared with patients not on ART (36).

1.5.4 Outcomes in MDR-TB/HIV co-infected patients based on the timing of initiation of ART

There have been few reported studies looking at the effect of timing of (early) initiation of ART on the outcomes of MDR-TB treatment in HIV positive patients (36, 38), but none in SSA. Palacios E et al. noted a lower death rate in HIV positive patients who had started ART early compared to those who were not on ART with receiving ART predicting a lower hazard of mortality (36). Nonetheless, the median time for ART initiation was longer, about 5.6 months, and this study had patients not on ART as a comparison group. Similar results were obtained in a study by Waisman JL et al. who compared mortality in MDR-TB HIV positive patients prior to availability of HAART and during the HAART era; with a limited sample size of 43 patients (37). These studies did not consider timing of ART based on before or after initiation of MDR-TB treatment. Early initiation of ART during MDR-TB treatment has been shown to produce favourable outcomes in terms of longer median survival time (20).

ART has been shown to confer a protective effect on mortality in HIV patients on MDR-TB treatment (36), and this evidence supports the current WHO guidelines on commencing ARTs within 2-8weeks after commencement of MDR-TB irrespective of the CD4 count (48), compared to that which was in operation prior to 2010 of which ART was initiated in patients with CD4 cell count less than 350 cells/mm3. Isaakidis P et al. reported improved overall outcomes with an increase in the median CD4 count (after one to two years of treatment) of co-infected patients, majority of who were on ART before initiation of MDR-TB treatment (38). Hence, adequate data is needed in SSA on the outcomes of MDR-TB in HIV positive patients who commenced ART before commencement of MDR-TB treatment compared to those who commenced ART after, to support the timely initiation of ART and improve the overall outcomes of MDR-TB in co-infected patients.

1.6 Study aim

The aim of the study was to determine the effect of timing of ART initiation on the treatment outcomes of MDR-TB in TB-HIV co-infected patients and the associated independent predictors of mortality, failure and cure.

1.6.1 Specific objectives

1. To describe the demographic and clinical characteristics of MDR-TB HIV co-infected patients initiated on ART before or after commencement of MDR-TB treatment at Sizwe Tropical Disease Hospital in Johannesburg, South Africa, from 1st January, 2007-31st December, 2010.

2. To determine and compare the outcomes of MDR-TB (cure, completed treatment, transferred out, defaulted, failed treatment, still on treatment and died) in HIV co-infected patients who were initiated on ART before and after commencement of MDR-TB treatment.

3. To investigate the relationship between varying time of receiving ART (before or after commencement of MDR-TB treatment) with cure, failure, and mortality adjusting for potential confounders such as age, BMI, haemoglobin level, CD4 count, the presence of fibrotic changes or cavities on chest radiographs and other opportunistic infections, etc.

CHAPTER 2: METHODS

In this chapter, the study design, study population and setting and selection of the study site, sampling and selection of the patient population, measurements and data sources are reviewed in detail. The key definitions, quality control, data management and analysis, and ethical considerations are also discussed.

2.1 Study design

This was a retrospective review of medical records of all HIV positive MDR-TB patients seen at Sizwe Tropical Disease Hospital, Johannesburg registered in the South African national MDR-TB program from 1st January, 2007 to 31st December, 2010.

2.2 Study setting

Sizwe Tropical Disease Hospital is situated at Edenvale and was established in 1895. In 2002, it became a specialised Provincial centre for the treatment of MDR-TB and in 2006, it was also mandated to treat XDR-TB following the emerging burden of DR-TB in South Africa. The hospital serves a vast majority of referred MDR/XDR-TB patients in Gauteng Province, who are treated as in- and out-patients.

The hospital has a total of eight wards comprising one admission ward, five MDR-TB adult wards, one paediatric ward, and one XDR-TB ward. There are 244 and 22 beds for MDR-TB and XDR-TB patients, respectively. All MDR-TB patients in the Province are admitted for initiation of treatment and subsequently discharged after culture conversion (two consecutive negative culture results taken 30 days apart) to decentralised care. About 75% of patients admitted for MDR-TB treatment at Sizwe hospital are HIV positive. Planned transportation services that carry patients to and from the hospital are available, and there is a tight follow-up and social welfare system to reduce the default rate.

2.3 Study population

The study population comprised all TB patients aged 18 years and older registered for MDR-TB treatment at Sizwe Tropical Disease Hospital in Johannesburg, South Africa from 1st January, 2007- 31st December, 2010.

2.4 Study sample

A total of 1,200 records of adult patients from the electronic database of Sizwe Tropical Disease Hospital suspected to be MDR-TB/HIV co-infected were reviewed over a four year period. The following eligibility criteria were applied to ensure that the study sample was correctly selected (see Figure 3.1).

2.4.1 Inclusion criteria:

These included patients on treatment for MDR-TB at Sizwe Tropical Disease Hospital who were:

- HIV positive adults aged 18 years and older,
- With confirmed drug susceptibility test results showing resistance to isoniazid and rifampicin.

2.4.2 Exclusion criteria:

- Patients younger than 18 years old.
- Patients who were HIV negative.
- Patients with no HIV test results or unknown HIV status.
- Individuals with missing records or case notes.
- Patients with earlier treatment dates before commencement of study.
- Those who died within 24 hours of treatment initiation and individuals who defaulted just after the first visit.

- Patients whose drug susceptibility tests (DST) were not confirmatory of MDR-TB (mono/poly resistance) and whose treatment were discontinued (pan susceptible patients).
- XDR-TB patients.

2.5 Data sources and measurement

Patients who were culture positive and confirmed to be having MDR-TB by DST or line probe assay (LPA) in all the sub-divisions of the National Health Service Laboratory (NHLS) throughout Gauteng province were referred from their clinics to Sizwe Tropical Disease Hospital. The NHLS performs culture and DST for DR-TB using liquid media such as BACTEC Mycobacterial Growth Indicator Tube (MGIT) 960 and Becton Dickinson which uses fluorescence quenching-based oxygen sensor for detection of mycobacterial growth.

Referred patients were first screened at Gateway clinic to ensure that results were suggestive or confirmatory of MDR-TB and initial registration was done for these patients. This was followed by a DST for all the first and second-line anti-tuberculous agents. Weight and height were measured for every patient before the start of MDR-TB treatment, except where patients were too ill to stand for the measurements. Baseline measurements of haemoglobin level, electrolytes, urea and creatinine, thyroid function test, liver function test, and CD4 cell count were also done prior to or during treatment.

Patients with unknown HIV status were referred to Thusong clinic for HIV counselling and testing. An initial rapid test was done and if reactive, a confirmatory Enzyme Linked Immuno-sorbent Assay (ELISA) followed. Newly diagnosed HIV patients were encouraged to initiate ART as soon as possible except where patients were too ill to commence treatment or declined initiation of ART**.** Prior to 2010, the WHO guideline for commencement of ART in patients with a confirmed diagnosis of DR-TB was based on a CD4 count of less than 350

cells/mm³. The guideline that followed regulated that patients be started on ART within 2-8 weeks, irrespective of the CD4 cell count (7, 48). Patients who were diagnosed to be HIV positive on admission and those already on ART were also referred to Thusong clinic for adherence counselling, continuous ARV administration and follow-up on HIV treatment.

The majority of the patients were started on the standardized regimen based on initial DST results (especially newly diagnosed MDR-TB patients); the choice for the next regimen was individualized based on follow-up DST results. Some patients' regimens were modified at baseline based on medical history, pre-existing adverse events and co-morbidities (called individualised regimen at baseline in this study). Patients were first commenced on the IP comprising KM/AM, MFX, ETO, TDR, and PZA taken at least six days a week for at least 6 months until after the first culture negative sputum.

Most of the patients were transferred to their local clinics with DOTS support groups who continued monitoring patients' treatment after one or two consecutive negative culture results. Adverse events, co-morbidities, and presence of opportunistic infections were managed and documented by clinicians during treatment and follow-up. Patients were given personal files which contained information on management at their local clinics and monthly sputum results for which they presented at the hospital during follow-up visits. The schedule for follow-up included: visits one month after discharge and subsequently 3 monthly with chest x-rays reviewed during each visit until the patient had completed treatment except where patients had other co-morbidities. Upon completion of treatment, patients were followed up 6 monthly for 2 years (a total of 4 visits after treatment completion) during which chest x-rays were done on each visits.

2.6 Data collection

Part of the data for this study comprised demographic and outcome records from the National TB registers. The data collected were for both HIV positive and HIV negative MDR-TB patients. The medical case files of HIV positive patients were reviewed for socio-demographic and clinical information not recorded on the TB register. Baseline x-rays of the patients were also reviewed. Data were entered into an Excel spreadsheet. Data collection started on the 14th November, 2013 and ended on the 21st February, 2014.

2.7 Outcome variable

The treatment outcomes of MDR-TB included: cure, completed treatment, defaulted, failed treatment, transferred out, still on treatment and died.

2.8 Exposure variables

The main exposure variable was receiving ART (before or after MDR-TB treatment initiation). Other exposure variables included the socio-demographic information like age, gender, employment status, race, and clinical information such as history of prior TB treatment, initial smear status, date of diagnosis of MDR-TB, days from diagnosis to MDR-TB treatment start, baseline DST result, duration on ART, baseline CD4 count, weight, height, BMI, haemoglobin level, baseline regimen, baseline chest radiographic findings, other opportunistic infections occurring during the course of treatment, presence of other co-morbidities, and adverse events.

2.9 Definition of study variables

2.9.1 Outcome variables

Definitions of MDR-TB treatment outcomes according to the WHO and South African Department of Health Drug-resistant TB Policy Guidelines 2013 (7, 49):

- Cure: A patient who has converted (with 2 consecutive TB culture negative taken 30 days apart), and has remained TB culture negative, has completed treatment and has been consistently culture-negative for five consecutive months in the final twelve months of treatment. If one positive culture is reported during that time and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least thirty days apart. This outcome is restricted to confirmed pulmonary DR-TB patients.
- Treatment completed: A patient who has completed treatment but does not meet the definition for cure due to lack of bacteriologic results (i.e. less than five cultures were performed in the final twelve months of treatment).
- Death: A patient who dies from any cause while on DR-TB treatment.
- Treatment default: A patient who interrupts DR-TB treatment for two or more consecutive months for any reason.
- Treatment failure: A patient who has had two or more of the five consecutive cultures taken in the final twelve months and are positive, or if any one of the final three cultures are positive. Treatment failure may be observed in patients who do not respond to treatment after 6 to 8 months of effective treatment. Such patients will be put on a different treatment regimen after receiving an outcome of failure and be allocated to a new treatment cohort.
- Transfer out: A patient who has been transferred to a reporting unit in another province and for whom the treatment outcome is unknown.
- Still on treatment: A patient who for any reason is still on treatment at the time of submission of treatment outcome report.
- Treatment success: The sum of cured and treatment completed.

2.9.2 Exposure variables

2.9.2.1 Socio-demographic variables

- Age: age of patient in years at time of start of MDR-TB treatment,
- Gender: gender of patient (male or female),
- Employment status: Employed or unemployed at initiation of MDR-TB treatment,
- Race: Black, White, Coloured, and Indian.

2.9.2.2 Clinical information

- Clinical characteristics of the cohort such as initial smear status (positive, negative, or not available), history of prior TB treatment also known as categories of MDR-TB (Category I: new patient who has received no anti-TB treatment for TB, MDR- or XDR-TB or received less than one month of anti-TB drug; category II: previously treated for one month or more with first-line drugs; category III: Previously treated for one month or more for TB or DR-TB with one or more of second-line drugs), baseline regimen (standardized: at least on 5 recommended drugs at baseline, individualised: modified regimen based on co-morbid conditions and adverse events with some drugs delayed), date of report of MDR-TB, date of start of MDR-TB treatment, duration on MDR-TB treatment, duration on ART (days), and the use of co-trimoxazole prophylaxis.

- Other variables included weight (Kilograms), height (meters), BMI-Kg/m² (severely underweight: <16, underweight: ≥16-18.49, normal: 18.5-24.99, overweight: 25-29.99 and obese: ≥30), baseline CD4 cell count (cells/mm³), haemoglobin level (g/dl), baseline chest radiographic findings (infiltrative lesions, cavitary, fibrosis or pleural effusion), presence of other opportunistic infections (such as oral or vaginal or oesophageal candidiasis, recurrent oral or genital Herpes simplex virus infection

(HSV), Pneumocystis Jirovecii Pneumonia (PCP), Herpes zoster infection, Cryptococcal infection, Cytomegalovirus (CMV) infection, cervical dysplasia or cancer, Kaposi sarcoma, HIV-associated nephropathy (HIVAN)).

- And finally co-morbidities (such as diabetes mellitus (DM), hypertension, cerebrovascular disease, heart failure, chronic kidney disease, chronic liver disease, asthma and chronic obstructive airway disease, cardiomyopathies and arrhythmias, deep venous thrombosis, sepsis, pancreatic disorders, cancers), and adverse events (ototoxicity, nephrotoxicity, hepatotoxicity, joint pains, severe gastrointestinal symptoms like nausea and vomiting requiring treatment, visual changes and conjunctivitis, psychosis, depression, peripheral neuropathy, hyperuricemia, hypothyroidism and gynaecomastia).

2.10.0 Data management

Data were entered into an Excel spread sheet separately for all the 4 years of the study. Inconsistencies were verified from case records and corrections were effected. The data were then transferred into STATA 12 for analysis. The data were cleaned by excluding individual records that did not meet the eligibility criteria (see Figure 3.1: flowchart); and missing data were checked for each variable. Continuous variables were recoded into categories for example age into age groups (≤45 years and >45 years), BMI (<16 kg/m² as severely underweight, ≥16-18.49 kg/m² as underweight, 18.50-24.99 kg/m² as normal, 25-29.99 kg/m² as overweight, ≥30 kg/m² as obese), CD4 (<150 cells/mm³, ≥150-349, ≥350), haemoglobin level (normal, mild, moderate and severe anaemia levels) to avoid residual confounding which may exist when such data are modelled as continuous.

New variables which were important for analyses were generated from existing data. The data for the four years were then appended to create a composite dataset which was used in the final analyses. Incomplete dates (day and months) were imputed for when patients experienced an outcome and date of ART initiation using the 15th of every month as day and mid-year (June) as months where only the year was recorded. Person times (treatment duration) were calculated from the dates of MDR-TB treatment initiation and outcomes. The variable ART duration was created from dates of commencement of ART and date of MDR-TB treatment initiation and those who commenced ART after MDR-TB treatment were categorized into immediate (≤28 days), early (29-56 days) and late (≥57 days) (22). Categorized variables with sparse numbers such as race were merged into black and others (white, coloured and Asian), and overweight and obese BMI were also merged into one category. Continuous data were checked for normality formally using the Shapiro-Wilk's test and graphically using histograms and normal quantile plots; as well as for skewness and kurtosis.

2.11.0 Data analysis

2.11.1 Descriptive and inferential statistics

Baseline demographic and clinical characteristics of the patients were described numerically using frequency distribution tables and graphically using bar or pie charts, and spine/tab plots for categorical data. Continuous data which followed a normal distribution were described numerically using means and standard deviations and median and interquartile ranges were used for non-normal and skewed data. Histograms were used to display continuous variables.

Baseline characteristics, clinical information and outcomes were compared between the two ART exposure groups excluding individuals who were not on ART or whose ART

information were not available. Pearson's chi-square test was used to compare categorical variables across the main exposure groups and Fisher's exact test was used where there were sparse data of ≤5 in 20% of the cells. Continuous variables which followed a normal distribution were compared using the student t-test and the Wilcoxon Rank-sum test used for non-normal/skewed data. All analyses were performed excluding missing data.

2.11.2 Assessment of effect modification and confounding

Stratified analyses were done for the three important outcomes: died, cure and failure with the main exposure and each of the covariates to check for effect modification and confounding. Variables with a significant Mantel-Haenszel's homogeneity p-value of <0.05 were considered as effect modifiers and those with greater than 10% difference between the crude and adjusted estimates were considered as confounders. These were considered for inclusion during the model building process of the final multivariable model.

2.11.3 Univariable and multivariable analyses

Univariable logistic regression analyses were done for all variables to determine the predictors of mortality, and cure. The low prevalence of patients, who failed treatment compared with the total study sample, necessitated the use of univariable Poisson regression to determine predictors of treatment failure. Statistically significant variables at a p-value of <0.1 and a priori biologically plausible covariates were considered important factors to be included in the multivariable regression analyses.

Multivariable logistic regression models were used to assess the effect of ART and other predictors of mortality and cure; while multivariable Poisson models were used for predictors of failure. A stepwise model building was done starting with the main exposure (ART timing) and subsequently including variables that were significant during the univariable analyses

while assessing the change in estimates. Variables were modelled either as categorical or continuous and interaction terms were included. Models were compared using the likelihood ratio test (lrtest), and Akaike International Criterion (AIC) to determine the best approach of including such variable or interaction term in the final multivariable model. Models with significant lrtest p-values or lower AIC were considered better than those with insignificant p-values or higher AIC. Potential confounders were adjusted for in the final multivariable models. Odds ratios were calculated for logistic models and incidence rate ratios (IRR) for Poisson models at 95% confidence interval and alpha level of <0.05.

Two models were built for mortality during the final multivariable analyses. Model 1: did not consider co-morbidity as an effect modifier; while for model 2 an interaction term was fit between the timing of ART initiation and presence of co-morbidity. There was no statistically significant interaction term between the timing of ART initiation and co-morbidity in the presence of other covariates; hence this model was dropped. Three models were also built for cure. Model one did not consider gender as an effect modifier. For model 2, an interaction term was fit between timing of ART and gender; while for model 3 an interaction term was fit with timing of ART and age groups, but this was not statistically significant. Model two was considered as the final and most parsimonious because there was a statistically significant interaction term between timing of ART regimen and gender. The final multivariable Poisson model for failure was specified using the vce-option (which uses the robust or sandwich estimator of variance) to obtain robust standard errors and to control for mild violation of the Poisson distribution assumptions, and these were comparable with results from the zero-inflated and negative binomial Poisson models. Time to event analysis was considered as a robust method for analysing this data, but the disparity in follow-up duration for the three major outcomes when others were considered to be censored did not allow the statistical method to fit the data well.

2.11.4 Model diagnostics

Model specification error was assessed using the link test command to ascertain that the linear predicted value and linear predicted value squared of the final models were correctly specified. A significant linear predictive value squared denotes a significant linktest and this depicts a specification error. The Box-Tidwell model (using the boxtid command) which transforms a predictor using power and exponential transformations were also used to find the best power for model fit based on maximum likelihood estimates. An insignificant p-value for the test of non-linearity depicts that the predictors be modelled as linear terms. The Hosmer-Lemeshow goodness-of-fit test was done for each model to assess any evidence of lack of fit. Multi-collinearity was assessed using the variance inflation factor (VIF) and tolerance level. Variables with VIF greater than 10 and tolerance level less than 0.1 were considered to be of perfect collinearity. Influential observations were assessed using the Pearson, deviance residuals and the Pregibon (hat diagonal) leverage. Sensitivity analysis were done for different models where observations with large leverage and residuals were removed and compared with original models with intact observations to assess for significant changes in estimates. All statistical analysis were done using STATA version 12.

2.12.0 Ethical considerations

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) in September, 2013. Ethical approval certificate is attached (see Appendix 1). Permission to review medical records was also granted by the Chief Executive Officer of Sizwe Tropical Disease Hospital (see Appendix 3).

CHAPTER 3: RESULTS

In this chapter the results are presented based on the study objectives and analysis plan. The demographic, clinical characteristics and outcomes of MDR-TB are reported. Predictors of mortality, cure and failure are summarised based on results from univariable and multivariable analyses.

3.1 Baseline characteristics

A total of 2,005 MDR-TB patients were admitted from 1st January, 2007 to 31st December, 2010. Of these, 1,200 adult patients had HIV positive status recorded on the database; 12 patients were excluded because laboratory records confirmed HIV negative status, and 2 patients had HIV status unknown during the course of treatment. In addition, 31 patients were excluded because their case files were missing, 7 patients were excluded on account of misdiagnosis (mono and poly-resistance); 4 patients had treatment start date prior to commencement of the study, 3 patients died within 24 hours of commencement of treatment and 2 treatment defaulters died after the first visit. Furthermore, 1 patient was excluded on account of XDR-TB and 1 was an infant aged 6 months. Therefore out of the 1,200 patients with data on HIV positive status, 1,137 patients met the eligibility criteria and were included in the analyses (see Figure 3.1).

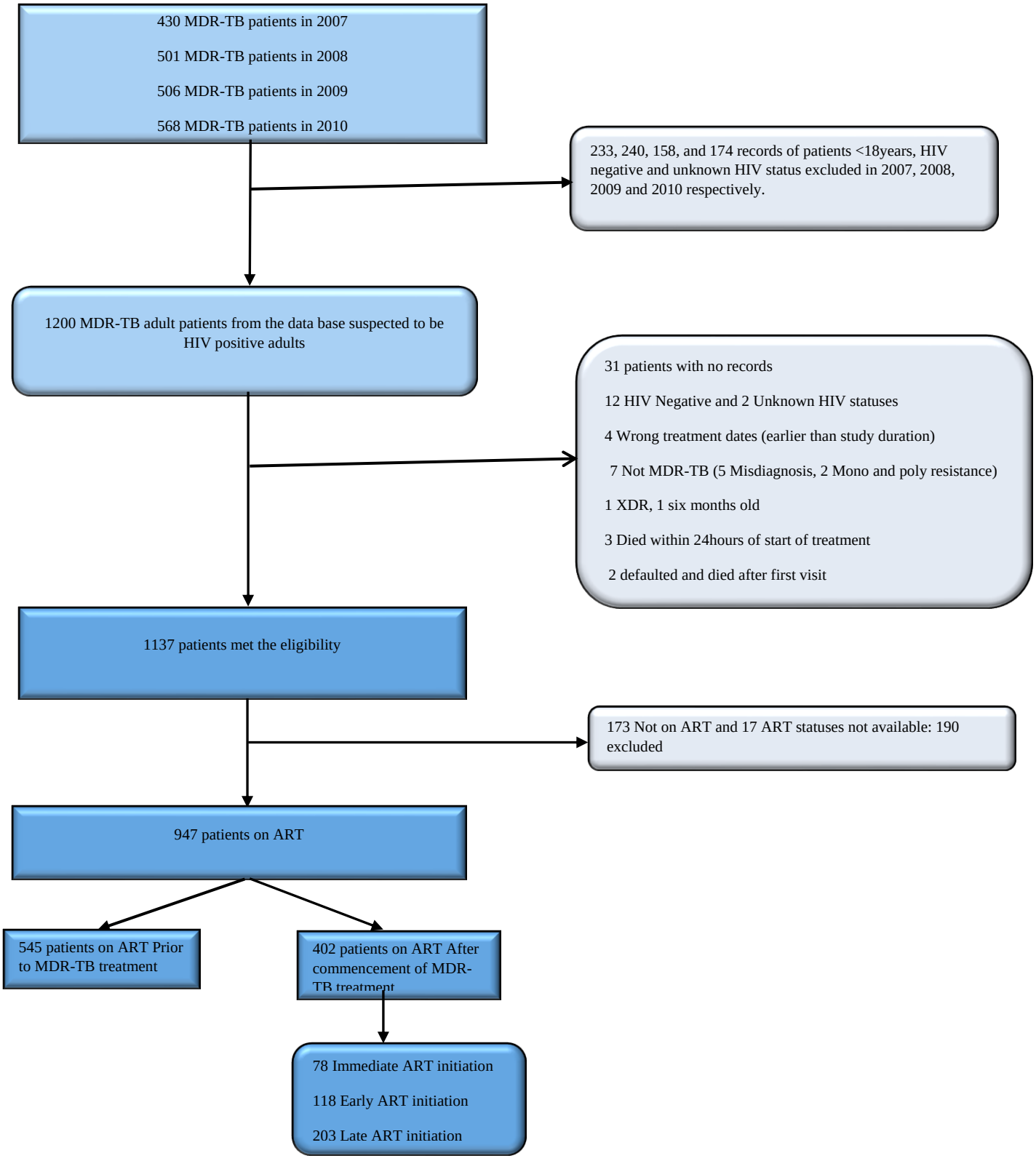


Figure 3.1: *Exclusion and inclusion criteria flowchart of the cohort.*

Tables 3.1.1 and 3.1.2 present the baseline characteristics of the study sample. The median age of patients was 36 years with an interquartile range (IQR) of 31-43 years and 50.2 % (572) were females. A total of 98.9% (1124) of the patients were blacks with 38.6% (439) living within the City of Johannesburg Metropolitan district. Of all patients, 72.4% (823) were unemployed. About 83% (940) of the patients had PTB, while 17.3% (197) had pulmonary and/or EPTB. Patients with category I (New) MDR-TB constituted 22.9% (260), while 57.6% (655) and 19.5% (222) of the patients were in categories II and III respectively as defined in the methods section. 58% of the patients had their pre-treatment smear results as positive, 30% had it as negative and 11% had no smear results. The median duration from diagnosis and report of MDR-TB infection by the NHLS laboratory across the province to the start of MDR-TB treatment was 10 days with IQR of 4-21 days. The mean haemoglobin was 11.1 g/dl with a standard deviation (SD) of 2.3 g/dl and the median CD4 count was 167.5 cells/mm^{3}with an IQR of 79-288 cells/mm^3.

Table 3.1.1: Baseline Demographic characteristics of HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital.

Factors	**N (%) (N = 1137)**
Age	36 (31-43)**
Gender	
Male	566 (49.8)
Female	571 (50.2)
District	
Westrand	137 (12.1)
Sedibeng	82 (7.2)
Tswhane	202 (17.8)
Ekhurhuleni	267 (23.5)
City of Johannesburg	439 (38.6)
Metsweding	10 (0.9)
Race	
Black	1124 (98.9)
Others	13 (1.1)
Employment status	
Employed	314 (27.6)
Unemployed	823 (72.4)

N - Number in each group; % - Percentages; * *Median and Interquartile range.

Table 3.1.2: Baseline clinical characteristics of HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital.

Factors	N (%) (N = 1137)
Categories of MDR-TB	
Category I (New)	260 (22.9)
Category II	655 (57.6)
Category III	222 (19.5)
Pre-treatment smear status	
Negative	345 (30.3)
Positive	666 (58.6)
Not available	126 (11.1)
Site of TB	
Pulmonary	940 (82.7)
Extra-Pulmonary + Pulmonary	197 (17.3)
Treatment outcomes	
Still on treatment	13 (1.1)
Transfer out	52 (4.6)
Treatment Defaulted	254 (22.3)
Treatment Completed	188 (16.5)
Cure	339 (29.8)
Failure	33 (2.9)
Died	258 (22.7)
Receiving ART	
After	402 (35.4)
Prior	545 (47.9)
No	173 (15.2)
Not available	17 (1.5)
ART duration	
Prior	491 (55.2)
Immediate (≤28days)	78 (8.8)
Early (29-56days)	118 (13.2)
Delayed (≥57days)	203 (22.8)
Weight (N = 1087)	51.3 (45.0-58.7)**
Weight categories (N = 1087)	
≤45kg	275 (25.3)
45.1-<60kg	562 (51.7)
≥60kg	250 (23.0)
BMI categories (kg/m^2)	
Severely Underweight (<16)	123 (10.8)
Underweight (≥16-18.49)	276 (24.3)
Normal (≥18.5-24.99)	435 (38.3)
Overweight/obese (≥25)	84 (7.4)
Missing	219 (19.3)
Co-trimoxazole Prophylaxis	
No	136 (12.0)
Yes	829 (72.9)
Missing	172 (15.1)

CD4 cell count (mls/mm³)	167.5 (79-288)**
CD4 Categories	
<150	485 (42.7)
150-349	398 (35.0)
≥350	193 (17.0)
Missing	61 (5.4)
Haemoglobin (g/dl)	11.1 (2.3)*
Haemoglobin categories (g/dl)	
Severe (≤7)	44 (3.9)
Moderate (7.1-9.99)	300 (26.4)
Mild (10-10.99)	175 (15.4)
Normal (≥11)	598 (52.6)
Missing	20 (1.8)
Outcome duration (days)	669 (236-880)**
Duration from report of MDR to start of treatment (days)	10 (4-21)**
Infiltrative changes on chest radiograph	
No	56 (5.1)
Yes	1,054 (94.9)
Cavitary change on chest radiograph	
No	637 (57.4)
Yes	473 (42.6)
Fibrotic changes on chest radiograph	
No	154 (13.9)
Yes	955 (86.1)
Pleural effusion on chest radiograph	
No	1,021 (92.1)
Yes	88 (7.9)
Other Opportunistic Infections	
No	752 (66.1)
Yes	381 (35.5)
Missing	4 (0.4)
Comorbidity	
No	965 (84.9)
Yes	150 (13.2)
Missing	22 (1.9)
Adverse events	
No	657 (57.8)
Yes	459 (40.4)
Missing	21 (1.9)
Regimen type at baseline	
Standardised	792 (69.7)
Individualised	328 (28.9)
Missing	17 (1.5)

N - Number in each group; % - Percentages; * *Median and Interquartile ranges; *Mean and standard deviation

Out of the 1,137 records included in the analysis, 1.1% (13) of the patients were still on treatment, 4.6% (52) were transferred out to other centres, 22.3% (254) defaulted treatment, 16.5% (188) completed treatment, 29.8% (339) were cured, 2.9% (33) failed treatment and 22.7% (258) died while on treatment (see Figure 3.1). Patients who commenced ART prior to commencement of MDR-TB treatment made up 47.9% of the entire population while 35.4% (402) started ART after commencement of MDR-TB treatment (see Appendix 5 for Figure 3.2). Of the 402 patients who started ART after initiating MDR-TB treatment, 8.8% (78) were commenced on ART within 28 days of initiating MDR-TB treatment; 13.3% (118) were initiated on ART within 29-56 days after commencing MDR-TB treatment and 22.8% (203) commenced ART after 57 days following MDR-TB treatment start. See Appendix 6 for Figure 3.3.

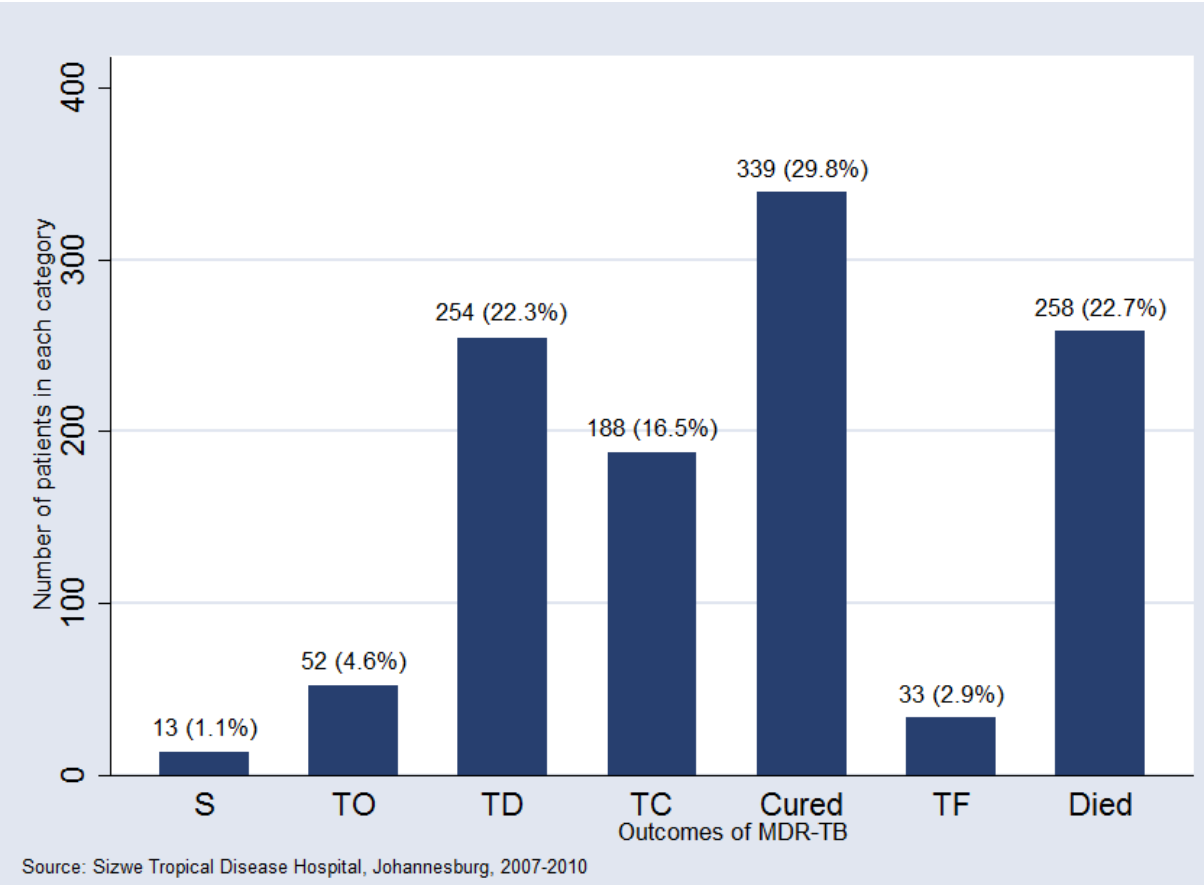


Figure 3.2: *Outcomes of MDR-TB treatments in HIV positive adults at Sizwe Tropical Disease Hospital from 1st January, 2007 to 31st December, 2010. S "Still on treatment"; TO "Transferred-out"; TD "Treatment Defaulted"; TC "Treatment Completed"; and TF "Treatment Failure".*

3.2 Inferential statistics

There was a statistically significant difference in the categories of MDR-TB among patients who started ART before and after initiation of MDR-TB treatment (p = 0.026), see Table 3.2.2. The proportion of new MDR-TB (category I) patients was higher among patients started on ART after initiating MDR-TB treatment (26.3% vs. 19.6); while those in categories II (58.7% vs. 62.0%) and III (14.7% vs. 18.4%) were similar between those started on ART after and before MDR-TB treatment initiation, respectively. EPTB/PTB was significantly higher among patients commenced on ART before compared with those started on ART after MDR-TB treatment initiation (20.73% vs. 13.93%, (p = 0.007)).

Compared with those started on ART after MDR-TB treatment initiation, more patients started on ART prior to commencement of MDR-TB treatment were on Co-trimoxazole prophylaxis (95.63% vs. 90.27%) and this was statistically significant (p = 0.003). The mean haemoglobin was significantly higher among patients who started ART prior to (11.32 (SD = 2.38)) compared with patients who commenced ART after MDR-TB treatment initiation (10.8 (SD = 2.2)), p = 0.001. This significant difference was also noticed among the different categories of haemoglobin (p = 0.009).

The presence of other non-TB opportunistic infections was higher among patients started on ART after commencement of MDR-TB treatment (42.9% vs. 26.6%, (p <0.001)) than in those on ART prior to commencement of MDR-TB treatment. A higher proportion of patients initiated on ART before commencement of MDR-TB treatment were on modified individualised regimen at baseline (31.5% vs. 24.9%, (p = 0.029)). The person time was significantly different amongst patients started on ART before and after MDR-TB treatment initiation with median duration of 251 days (IQR = 90-725) and 720 days (IQR = 330-945) for both groups respectively, (p = 0.029). See Table 3.2.2.

Table 3.2.2: **Bivariate analysis of clinical characteristics of MDR-TB HIV co-infected adults based on exposure to ART before or after commencement of MDR-TB treatment.**

Factors	ART prior to commencement of MDR-TB treatment N (%) (N= 545)	ART after commencement of MDR-TB treatment N (%) (N= 402)	Test Statistic	p-value
Categories of MDR-TB				
Category I (New)	107 (19.6)	107 (26.6)	Chi = 7.270	0.026*
Category II	338 (62.0)	236 (58.7)		
Category III	100 (18.4)	59 (14.7)		
Pre-treatment smear status				
Negative	166 (30.5)	134 (33.3)	Chi = 1.038	0.595
Positive	317 (58.2)	221 (55.0)		
Not available	62 (11.4)	47 (11.7)		
Site of TB				
Pulmonary	432 (79.3)	346 (86.1)	Chi = 7.304	0.007*
Extra-Pulmonary + Pulmonary	113 (20.7)	56 (13.9)		
Treatment outcomes				
Still on treatment	5 (0.9)	8 (2.0)	Chi = 10.770	0.096
Transfer out	26 (4.8)	18 (4.5)		
Treatment Defaulted	105 (19.3)	101 (25.1)		
Treatment Completed	92 (16.9)	71 (17.7)		
Cure	182 (33.4)	130 (32.3)		
Failure	16 (2.9)	12 (3.0)		
Died	119 (21.8)	62 (15.4)		
Combining cure and TC as Successful treatment				
Still on treatment	5 (0.9)	8 (2.0)	Chi = 10.614	0.060
Transfer out	26 (4.8)	18 (4.5)		
Treatment Defaulted	105 (19.3)	101 (25.1)		
Successful Treatment	274 (50.3)	201 (50.0)		
Failure	16 (2.9)	12 (3.0)		
Died	119 (21.8)	62 (15.4)		
Weight (Kg)	51.0 (45-59)**	51.2 (45-58)**	z = -0.249	0.803
Weight categories				
≤45kg	134 (25.9)	106 (26.5)	Chi = 0.071	0.965
45.1-<60kg	263 (50.8)	203 (50.8)		
≥60kg	121 (23.3)	91 (22.7)		
BMI categories (Kg/ m^2)				
Severely Underweight (<16)	68 (15.4)	41 (11.4)	Chi = 4.963	0.174
Underweight (≥16-18.49)	130 (29.4)	111 (31.0)		
Normal (≥18.5-24.99)	195 (44.1)	176 (49.2)		

Overweight/ obese (25-29.99)	49 (11.1)	30 (8.4)		
Co-trimoxazole Prophylaxis				
No	21 (4.4)	32 (9.7)	Chi = 9.131	0.003*
Yes	459 (95.6)	297(90.3)		
CD4 cell count (mls/mm³)	160.5 (89-270)**	156 (66-257)**	z = -1.309	0.1906
CD4 Categories (mls/mm³)				
<150	241 (46.5)	187 (48.1)	Chi = 2.434	0.296
150-349	209 (40.4)	140 (36.0)		
≥350	68 (13.1)	62 (15.9)		
Haemoglobin (g/dl)	11.3 (2.4)*	10.8(2.2)*	t = -3.246	0.0012*
Haemoglobin (g/dl)				
Severe Anaemia (<7.0)	24 (4.5)	13 (3.3)	Chi = 11.677	0.009*
Moderate Anaemia (7.0-9.9)	120 (22.3)	123 (31.0)		
Mild Anaemia (10-10.99)	85 (15.8)	70 (17.7)		
Normal (≥11)	308 (57.4)	190 (48.0)		
Outcome duration or Person time (days)	251 (90- 725)**	720 (330-945)**	z = 2.188	0.0286*
Duration from report of MDR to start of treatment (days)	11 (5-22)**	10 (6-21)**	z = -0.099	0.921
Infiltrative changes on chest radiograph				
No	24 (4.5)	11 (2.8)	Chi = 1.806	0.179
Yes	513 (95.5)	385 (97.2)		
Cavitary change on chest radiograph				
No	315 (58.7)	237 (59.8)	Chi = 0.133	0.715
Yes	222 (41.3)	159 (40.2)		
Fibrotic changes on chest radiograph				
No	77 (14.3)	58 (14.7)	Chi = 0.0218	0.883
Yes	460 (85.7)	337 (85.3)		
Pleural effusion on chest radiograph				
No	491 (91.4)	364 (92.2)	Chi = 0.155	0.694
Yes	46 (8.6)	31 (7.8)		
Other Opportunistic Infections				
No	399 (73.4)	228 (57.1)	Chi = 27.121	<0.001*
Yes	145 (26.6)	171 (42.9)		
Comorbidity				
No	461 (85.8)	345 (88.0)	Chi = 0.923	0.337
Yes	76 (14.2)	47 (12.0)		
Adverse events				
No	295 (54.8)	239 (61.1)	Chi = 3.669	0.055
Yes	243 (45.2)	152 (38.9)		
Regimen type at baseline				
Standardised	370 (68.5)	295 (75.1)	Chi = 4.759	0.029*
Individualised	170 (31.5)	98 (24.9)		

N - Total number in each group; % - Column percentages; Numbers may not add-up to total because of missing variables; *Significant p-value, Mean and Standard Deviation;
**Median and Inter-quartile ranges.

Test statistic based on t-test, chi-square and Wilcoxon Rank-sum test.

3.3 Outcomes of MDR-TB by ART treatment groups

Treatment outcomes were not significantly different between patients on ART before and after commencement of MDR-TB treatment (p = 0.096), see Table 3.2.3. When the analysis was restricted to patients who died, the proportion of mortality was higher for those on ART prior to commencement of MDR-TB treatment (21.8% vs. 15.4%, (p = 0.013)). See Appendix 7 for Figure 3.4.

Table 3.2.3: Bivariate analysis of outcomes of MDR-TB in HIV co-infected adults based on commencement of ART prior to or after MDR-TB treatment initiation.

Factors	ART Prior to commencement of MDR-TB treatment N (%)	ART After commencement of MDR-TB treatment N (%)	Test Statistic	p-value
Final Outcomes				
Still on treatment	5 (0.9)	8 (2.0)	Chi = 10.771	0.096
Transferred out	26 (4.8)	18 (4.5)		
Treatment Defaulted	105 (19.3)	101 (25.1)		
Treatment Completed	92 (16.9)	71 (17.7)		
Cure	182 (33.4)	130 (32.3)		
Failure	16 (2.9)	12 (3.0)		
Died	119 (21.8)	62 (15.4)		
Died				
No	426 (78.2)	340 (84.6)	Chi = 6.153	0.013*
Yes	119 (21.8)	62 (15.4)		
Cure				
No	363 (66.6)	272 (67.7)	Chi = 0.117	0.733
Yes	182 (33.4)	130 (32.3)		
Failure				
No	529 (97.1)	390 (97.0)	Chi = 0.002	0.965
Yes	16 (2.9)	12 (3.0)		
Total	**545**	**402**		

N - Total number in each group; % - Column percentages; Test statistic = Chi-square test.
*Significant p-value.

3.4 Assessment of effect modification and confounding

3.4.1 Mortality

In the stratified analyses for mortality, the presence of co-morbidities during MDR-TB treatment modified the relationship between timing of ART initiation and mortality (Mantel-Haenszel homogeneity p-value of 0.019). Haemoglobin confounded the relationship between the use of ART prior to or after commencement of MDR-TB treatment by 17.7%; while the categories of CD4 cell count, BMI and the presence of other opportunistic infections confounded the relationship by 12.1%, 18.6%, and 21.9%, respectively.

3.4.2 Cure

Gender was an effect modifier in the relationship between timing of ART initiation and cure ($p = 0.008$) and so was age-group ($p = 0.013$).

3.4.3 Failure

The use of Co-trimoxazole prophylaxis during MDR-TB treatment confounded the relationship between the use of ART before or after commencement of MDR-TB treatment and failure by 14.0%.

3.5 Predictors of mortality

3.5.1 Univariable logistic regression models

Significant predictors of mortality (Table 3.3) were being unemployed, patients started on ART before commencement of MDR-TB treatment, being severely underweight and underweight, CD4 <150 cells/mm^3, low haemoglobin, the presence of other opportunistic infections, co-morbidities, adverse-events, and PTB and/or EPTB.

3.5.1.1 Socio-demographic factors

- Patients who were unemployed were 1.6 times more likely to die compared with patients who were employed (OR: 1.64; 95% CI: 1.12-2.44; p = 0.014).

3.5.1.2 Clinical factors

Patients who used ART before commencement of MDR-TB treatment were more likely to die compared with those on ART after starting MDR-TB treatment (OR: 1.53; 95% CI: 1.09-2.15; p = 0.014). Patients who were severely underweight were 4.6 times more likely to die (OR: 4.61; 95% CI: 2.77-7.68; p <0.001) and those who were underweight were twice as likely to die (OR: 2.33; 95% CI: 1.49-3.65; p <0.001) when both were compared with patients with normal BMI. Those with CD4 count <150 cells/m³ were nearly three time as likely to die compared with patients with CD4 count >350 cells/m³ (OR: 2.88; 95% CI: 1.62-5.14; p <0.001). For every unit increase in haemoglobin, there was a 0.8 decrease in odds of mortality (OR: 0.76; 95% CI: 0.70-0.82; p <0.001) and this was reflected in the different categories of haemoglobin. Those with other opportunistic infections were 2.5 times more likely to die compared with patients with no other opportunistic infections (OR: 2.54; 95% CI: 1.82-5.97; p <0.001).

Patients with Co-morbidities were nearly 4 times more likely to die compared with patients without other co-morbidities (OR: 3.97; 95%CI: 2.64-5.97; p <0.001). Individuals with the presence of adverse events were 1.5 times more likely to die compared with those with no adverse events during treatment (OR: 1.45; 95% CI: 1.04-2.02; p = 0.028). Compared with standardised regimen at baseline, patients on individualised regimen were 1.6 times more likely to die (OR: 1.55; 95% CI: 1.10-2.19; p = 0.013). Patients with EPTB with/or without PTB were 1.4 times more likely to die compared with patients with PTB only (OR: 1.40; 95% CI: 0.94-2.09; p = 0.098); while patients previously treated with second-line agents (category

III) were less-likely to die compared with patients not previously treated for TB or MDR-TB (OR: 0.59; 95% CI: 0.33-1.05; p = 0.073).

3.5.2 Multivariable logistic model

3.5.2.1 Clinical factors

Patients who received ART prior to commencement of MDR-TB treatment were 1.8 times more likely to die compared with those who commenced ART after initiation of MDR-TB treatment (OR: 1.76; 95% CI:1.07-2.91; p = 0.026), adjusting for confounders such as BMI, haemoglobin, CD4 cell count and the presence of other opportunistic infections. Compared with normal BMI, those who were severely underweight (OR: 3.46; 95% CI: 1.77-6.77; p <0.001) and underweight (OR: 2.31; 95% CI: 1.28-4.15; p = 0.005) were more likely to die. See Table 3.3.

Patients with the presence of cavitary lesions on baseline chest x-ray were 1.8 times more likely to die (OR: 1.83; 95% CI: 1.13-2.96; p = 0.014) compared with patients without cavitary lesions. Those with the presence of other opportunistic infections had a higher odds of mortality compared with patients without other opportunistic infections (OR: 1.84; 95% CI: 1.13-3.00; p = 0.014). Compared with patients without co-morbidity, individuals with co-morbidities were 2.5 times more likely to die (OR: 2.51; 95% CI: 1.34-4.68; p = 0.004).

There was a trend with factors such as haemoglobin (OR: 0.89; 95% CI [0.79-1.00]; p = 0.060) with reduced odds of mortality for every unit increase in haemoglobin; although this was not statistically significant. There was no statistically significant interaction between timing of ART initiation and co-morbidity (p = 0.229) with an lrtest p = 0.220; hence the model with the interaction term was dropped. There were no highly correlated variables and no evidence of lack of fitness of the final model as the Hosmer-Lemeshow goodness-of-fit p-value was 0.449. The model was correctly specified (specification error p = 0.529). The

variable haemoglobin was correctly modelled as a linear term (non-linearity p = 0.200), and the VIF and tolerance levels were all within normal limits. Removal of observations with large Pearson and deviance residuals as well as influential points did not significantly change the estimates from the previous models.

Table 3.3: Predictors of mortality in HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Factor	[a]Univariable Analysis			[b]Multivariable Analysis		
	Unadjusted OR	**Confidence interval**	**p-value**	**Adjusted OR**	**Confidence interval**	**p-value**
ART regimen						
After	1.00	Ref		1.00	Ref	
Prior	1.53	1.09-2.15	0.014*	1.76	1.07-2.91	0.026*
Age	1.01	0.99-1.03	0.481			
Gender						
Female	1.00	Ref		1.00	Ref	
Male	1.08	0.78-1.49	0.661	1.52	0.91-2.55	0.110
District						
Westrand	1.00	Ref				
Sedibeng	0.87	0.39-1.95	0.740			
Tswhane	1.10	0.60-2.03	0.753			
Ekhurhuleni	0.94	0.51-1.70	0.826			
City of Johannesburg	1.24	0.72-2.14	0.440			
Metsweding	1.53	0.29-8.16	0.616			
Race						
Other	1.00	Ref				
Black	0.78	0.21-2.88	0.715			
Employment status						
Employed	1.00	Ref				
Unemployed	1.64	1.12-2.44	0.014*			
Categories of MDR-TB						
Category I (New)	1.00	Ref				
Category II	1.07	0.72-1.59	0.732			
Category III	0.59	0.33-1.05	0.073			
Pre-treatment smear status						
Negative	1.00	Ref				
Positive	1.34	0.93-1.92	0.113			
Not available	0.54	0.27-1.07	0.076			
Site of TB						
Pulmonary	1.00	Ref				
Extra-Pulmonary + Pulmonary	1.40	0.94-2.09	0.098			
BMI categories (kg/m^2)						
Severely Underweight (<16)	4.61	2.77-7.68	<0.001*	3.46	1.77-6.77	<0.001*
Underweight (≥16-18.49)	2.33	1.49-3.65	<0.001*	2.31	1.28-4.15	0.005*

Normal (≥18.5-24.99)	1.00	Ref		1.00	Ref	
Overweight/ obese (25-29.99)	1.20	0.57-2.51	0.630	2.28	0.94-5.50	0.067
Co-trimoxazole Prophylaxis						
No	1.00	Ref		1.00	Ref	
Yes	1.33	0.62-2.89	0.464	1.27	0.47-3.48	0.639
CD4 Categories (mls/mm³)						
<150	2.88	1.62-5.14	<0.001*	1.62	0.77-3.48	0.213
150-349	0.91	0.48-1.72	0.770	0.64	0.28-1.43	0.275
≥350	1.00	Ref		1.00	Ref	
Haemoglobin (g/dl)	0.76	0.70-0.82	<0.001*	0.89	0.79-1.00	0.060
Infiltrative changes on chest radiograph						
No	1.00	Ref				
Yes	0.74	0.33-1.67	0.470			
Cavitary changes on chest radiograph						
No	1.00	Ref		1.00	Ref	
Yes	1.25	0.89-1.74	0.191	1.83	1.13-2.96	0.014*
Fibrotic changes on chest radiograph						
No	1.00	Ref				
Yes	1.17	0.71-1.91	0.527			
Other Opportunistic Infections						
No	1.00	Ref		1.00	Ref	
Yes	2.54	1.82-3.55	<0.001*	1.84	1.13-3.00	0.014*
Comorbidity						
No	1.00	Ref		1.00	Ref	
Yes	3.97	2.64-5.97	<0.001*	2.51	1.34-4.68	0.004*
Adverse events						
No	1.00	Ref		1.00	Ref	
Yes	1.45	1.04-2.02	0.028*	1.07	0.67-1.73	0.771
Regimen type at baseline						
Standardised	1.00	Ref				
Individualised	1.55	1.10-2.19	0.013*			

*Significant p-values; OR: Odds ratios; Hosmer-Lemeshow Goodness-of-fit test p = 0.4489;
Model specification test p = 0.529;
[a]Unadjusted model; [b]Adjusted for BMI, haemoglobin, CD4, and other opportunistic infections.

3.6 Predictors of cure

3.6.1 Univariable analyses

The following factors were predictors of cure during the univariable analyses (see Table 3.4):

3.6.1.1 Socio-demographic factors

Patients in the age group 46-76 years were 1.6 times more likely to be cured compared with those in the younger age group (OR: 1.59; 95% CI: 1.13-2.45; p = 0.008). Patients from Johannesburg Metropolitan district (OR: 0.63; 95% CI: 0.41-0.99; p = 0.043) and Ekhurhuleni district (OR: 0.63; 95% CI: 0.39-1.01; p = 0.056) were less likely to be cured compared with patients from the Westrand district. Unemployed patients were 0.8 times less likely to be cured compared with those who were employed (OR: 0.75; 95% CI: 0.56-1.02; p = 0.063).

3.6.1.2 Clinical factors

Compared with patients with CD4 count "<150 cells/m³", those with CD4 cell counts between "150-349 cells/m³" (OR: 1.42; 95% CI: 1.05-1.92; p = 0.023) and "≥350 cells/m³" (OR: 1.58; 95% CI: 1.05-2.38; p = 0.028) were more likely to be cured. Patients with the presence of other opportunistic infections were 0.7 times less likely to be cured compared with patients without other opportunistic infections (OR: 0.66; 95% CI: 0.49-0.89; p = 0.007). The presence of other co-morbidities was associated with lower likelihood of cure compared with absence of other co-morbidities (OR: 0.59; 95% CI: 0.38-0.91; p = 0.018). Individualised regimen at baseline compared with standardized regimen was associated with lower likelihood of cure (OR: 0.67; 95% CI: 0.49-0.91; p = 0.012).

Patients with infiltrative changes on chest radiograph were 2.5 times more likely to be cured compared with those without infiltrative lesions (OR: 2.50; 95% CI: 1.03-6.08; p = 0.044). Cavitary changes on chest x-ray was associated with decrease likelihood of cure compared

with other x-ray findings (OR: 0.67; 95% CI: 0.51-0.89; p = 0.006). There was a statistically significant interaction term between gender and timing of ART. Males who were on ART prior to MDR-TB treatment were 2.1 times more likely to be cured compared with females started on ART after initiating MDR-TB treatment (OR: 2.12; 95% CI: 1.22-3.69; p = 0.008). Patients with normal haemoglobin level were twice as likely to be cured compared with those who were severely anaemic (OR: 2.02; 95% CI: 0.90-4.51; p = 0.087).

3.6.2 Multivariable logistic model

3.6.2.1 Socio-demographic/clinical factors

Female patients on ART before commencement of MDR-TB treatment were 0.6 times less likely to be cured compared with females who were initiated on ART after the start of MDR-TB treatment, adjusting for confounders such as age, BMI, co-morbidity, etc. (OR: 0.63; 95% CI: 0.39-1.02; p = 0.060) even though this was not statistically significant. Male patients on ART after commencement of MDR-TB treatment were 0.5 times less likely to be cured compared with females started on ART after MDR-TB treatment initiation, keeping all other covariates constant (OR: 0.46; 95% CI: 0.26-0.80; p = 0.006). Male patients who were on ART before commencement of MDR-TB treatment (OR: 2.97; 95%CI: 1.47-5.99; p = 0.002) were nearly three times as likely to be cured compared with females who were started on ART after MDR-TB treatment initiation, adjusting for age, BMI, co-morbidity, co-trimoxazole prophylaxis, etc. See Appendix 8, Table 3.6.1 for predicted log-odds.

Individuals aged 46 years and older were 1.7 times more likely to be cured compared with the younger age group (OR: 1.65; 95% CI: 1.05-2.59; p = 0.030). Patients with CD4 cell count between “150-349” cells/m³ (OR: 1.85; 95% CI: 1.26-2.72; p = 0.002) and “≥350” cells/mm³ (OR: 1.76; 95%CI: 1.02-3.04; p = 0.043) were more likely to be cured compared with patients with CD4 cell count <150 cells/m³ (See Table 3.4). Those who had cavitary changes

on chest x-ray were 0.6 times less likely to be cured compared with patients with other x-ray findings (OR: 0.55; 95% CI: 0.39-0.79; p = 0.001). There was a decrease in likelihood of cure for patients who were placed on individualised regimen at baseline compared with patients on standardised regimen (OR: 0.62; 95% CI: 0.42-0.92; p = 0.016).

There was no evidence of lack of fit of the model (Hosmer-Lemeshow goodness-of-fit p = 0.359). There was no evidence of misspecification of the model (p = 0.653). BMI and haemoglobin were correctly modelled as linear terms (non-linearity p = 0.063 and 0.158 respectively). There was no evidence of multi-collinearity as the VIF and tolerance levels were within normal ranges. Sensitivity analysis was done with observations with high Pearson residuals and high leverage removed and model did not differ significantly from that with intact observations.

Table 3.4: Predictors of cure in HIV positive adults on treatment for MDR-TB at Sizwe Tropical Disease Hospital, Johannesburg.

Factor	[a]Univariable Analysis			[b]Multivariable Analysis		
	Unadjusted OR	Confidence interval	p-value	Adjusted OR	Confidence interval	p-value
ART regimen						
After	1.00	Ref		1.00	Ref	
Prior	1.05	0.79-1.38	0.733	0.63	0.39-1.02	0.060
Gender						
Female	1.00	Ref				
Male	0.92	0.70-1.20	0.528	0.46	0.26-0.80	0.006*
ART regimen#gender						
After#Females	1.00	Ref		1.00	Ref	
Prior#Males	2.12	1.22-3.69	0.008*	2.97	1.47-5.99	0.002*
Age groups						
18-45	1.00	Ref		1.00	Ref	
46-76	1.59	1.13-2.45	0.008*	1.65	1.05-2.59	0.030*
District						
Westrand	1.00	Ref				
Sedibeng	0.90	0.49-1.67	0.738			
Tswhane	0.85	0.53-1.39	0.524			
Ekhurhuleni	0.63	0.39-1.01	0.056			
City of Johannesburg	0.63	0.41-0.99	0.043*			
Metsweding	0.89	0.20-3.93	0.881			
Race						
Other	1.00	Ref				
Black	0.57	0.19-1.71	0.314			
Employment status						
Employed	1.00	Ref				
Unemployed	0.75	0.56-1.02	0.063			
Categories of MDR-TB						
Category I (New)	1.00	Ref				
Category II	0.88	0.63-1.22	0.444			
Category III	1.02	0.67-1.58	0.898			
Pre-treatment smear status						
Negative	1.00	Ref				
Positive	0.80	0.59-1.07	0.136			
Not available	0.72	0.45-1.53	0.171			
Site of TB						
Pulmonary	1.00	Ref				
Extra-Pulmonary + Pulmonary	0.86	0.60-1.23	0.398			
BMI (kg/m²)	1.03	0.99- 1.07	0.134	1.00	0.95-1.05	0.996
Co-trimoxazole Prophylaxis						
No	1.00	Ref		1.00	Ref	

Yes	1.39	0.74-2.61	0.302	1.43	0.70-2.91	0.320
CD4 Categories (cell/mm³)						
<150	1.00	Ref		1.00	Ref	
150-349	1.42	1.05-1.92	0.023*	1.85	1.26-2.72	0.002*
≥350	1.58	1.05-2.38	0.028*	1.76	1.02-3.04	0.043*
Haemoglobin (g/dl)	1.07	1.01-1.34	0.030*	0.98	0.90-1.07	0.707
Infiltrative changes on chest radiograph						
No	1.00	Ref				
Yes	2.50	1.03-6.08	0.044*			
Cavitary changes on chest radiograph						
No	1.00	Ref		1.00	Ref	
Yes	0.67	0.51-0.89	0.006*	0.55	0.39-0.79	0.001*
Fibrotic changes on chest radiograph						
No	1.00	Ref				
Yes	0.83	0.57-1.22	0.344			
Other Opportunistic Infections						
No	1.00	Ref				
Yes	0.66	0.49-0.89	0.007*			
Comorbidity						
No	1.00	Ref		1.00	Ref	
Yes	0.59	0.38-0.91	0.018*	0.61	0.35-1.08	0.092
Adverse events						
No	1.00	Ref				
Yes	1.06	0.81-1.40	0.668			
Regimen type at baseline						
Standardised	1.00	Ref		1.00	Ref	
Individualised	0.67	0.49-0.91	0.012*	0.62	0.42-0.92	0.016*

*Significant p-values; OR: Odds ratio; ART regimen#gender: Interaction between timing of ART and gender;
Hosmer-Lemeshow Goodness-of-fit test p = 0.359;
Model specification test p = 0.653;
[a]Unadjusted models; [b]Adjusted for age, BMI, co-morbidity, CTX prophylaxis.

3.7 Predictors of failure

3.7.1 Univariable Poisson regression analysis

3.7.1.1 Clinical factor

The only factor that was associated with failure during the univariable analyses was individualised regimen at baseline (see Table 3.5). Compared with standardised regimen at baseline, patients on individualised regimen at baseline had over two times the higher rate of failure (IRR: 2.48; 95% CI: 1.18-5.20; p = 0.016).

3.7.2 Multivariable Poisson analysis

3.7.2.1 Clinical factors

There was no statistically significant relationship between receiving ART prior to MDR-TB treatment and incidence rate ratio of failure (IRR: 0.75; 95% CI: 0.33-1.73; p = 0.504), keeping all other covariates constant. Patients with severe anaemia had nearly 4 times higher rate of failure compared with patients with normal haemoglobin level (IRR: 3.94; 95% CI: 1.20-12.89; p = 0.024). Patients on individualised regimen at baseline had a 2.3 times higher rate of failure compared with patients on standardized regimen at baseline (IRR: 2.25; 95% CI: 1.02-4.95; p = 0.045). There was a trend with factors such as presence of co-morbidity (IRR: 2.20; 95% CI: 0.95-5.11; p = 0.067) and cavitary lesions on chest x-ray (IRR: 2.12; 95% CI: 0.93-4.83; p = 0.075) with p-values greater than 0.05, but less than 0.1 to be predictors of failure (see Table 3.5). There were no highly correlated variables during the assessment of multi-collinearity. Haemoglobin and BMI were modelled as linear terms as non-linearity p-values were 0.553 and 0.570 respectively. There was no evidence of specification error (p = 0.969) nor lack of fit of the model (Pearson goodness-of-fit p = 0.504).

Table 3.5: Predictors of failure in HIV positive adults on MDR-TB treatment at Sizwe Tropical Disease Hospital, Johannesburg.

Factor	[a]Univariable Analysis			[b]Multivariable Analysis		
	Unadjusted IRR	Confidence interval	p-value	Adjusted IRR	Confidence interval	p-value
ART regimen						
After	1.00	Ref		1.00	Ref	
Prior	0.98	0.47-2.00	0.965	0.75	0.33-1.73	0.504
Age groups						
18-45	1.00	Ref				
46-76	0.79	0.27-2.28	0.662			
Gender						
Female	1.00	Ref				
Male	0.93	0.44-1.96	0.854			
Employment status						
Employed	1.00	Ref				
Unemployed	0.94	0.41-2.13	0.875			
Categories of MDR-TB						
Category I (New)	1.00	Ref		1.00	Ref	
Category II	2.05	0.71-5.95	0.186	1.58	0.49-5.16	0.446
Category III	0.67	0.12-3.67	0.647	0.44	0.05-4.08	0.669
Pre-treatment smear status						
Negative	0.61	0.15-2.53	0.492			
Positive	1.35	0.40-4.55	0.627			
Not available	1.00	Ref				
Site of TB						
Pulmonary	1.00	Ref				
Extra-Pulmonary + Pulmonary	0.77	0.27-2.21	0.624			
BMI	0.97	0.87-1.07	0.547	1.01	0.93-1.09	0.893
Co-trimoxazole Prophylaxis						
No	1.00	Ref		1.00	Ref	
Yes	0.88	0.21-3.70	0.857	1.59	0.25-10.30	0.626
CD4 (Cells/mm3)						
<150	0.76	0.29-1.96	0.569			
150-349	0.43	0.15-1.29	0.134			
≥350	1.00	Ref				
Haemoglobin (g/dl)						
Severe Anaemia (<7.0)	2.69	0.78-9.30	0.117	3.94	1.20-12.89	0.024*
Moderate Anaemia (7.0-9.99)	1.09	0.46-2.57	0.839	0.96	0.40-2.31	0.922
Mild Anaemia (10-10.99)	0.43	0.10-1.87	0.260	0.25	0.03-1.78	0.164
Normal (≥11)	1.00	Ref		1.00	Ref	
Infiltrative changes on chest radiograph						
No	1.00	Ref				
Yes	1.01	0.14-7.47	0.990			
Cavitary changes on chest						

radiograph						
No	1.00	Ref		1.00	Ref	
Yes	1.81	0.85-3.87	0.125	2.12	0.93-4.83	0.075
Fibrotic changes on chest radiograph						
No	1.00	Ref				
Yes	1.36	0.41-4.50	0.620			
Other Opportunistic Infections						
No	1.00	Ref				
Yes	0.94	0.43-2.08	0.878			
Comorbidity						
No	1.00	Ref		1.00	Ref	
Yes	1.79	0.72-4.41	0.207	2.20	0.95-5.11	0.067
Adverse events						
No	1.00	Ref		1.00	Ref	
Yes	0.54	0.24-1.23	0.142	0.50	0.22-1.44	0.100
Regimen type at baseline						
Standardised	1.00	Ref		1.00	Ref	
Individualised	2.48	1.18-5.20	0.016*	2.25	1.02-4.95	0.045*

IRR- Incidence rate ratio; *Significant p-values; Pearson goodness-of-fit p = 0.504;
Model specification test p = 0.969
[a]Unadjusted models; [b]Adjusted for Co-trimoxazole prophylaxis.

CHAPTER 4: DISCUSSION

4.1 Introduction

The demographic, clinical characteristics and outcomes of MDR-TB in HIV co-infected patients at Sizwe Tropical Disease Hospital were examined based on timing of ART initiation, as well as predictors of mortality, cure and failure. A total of 1,137 patients were included in the preliminary analyses with the proportion of patients with no history of previous TB and MDR-TB treatment (primary MDR-TB) among this population being 22.9%. The median duration from report of MDR-TB by the NHSL to start of MDR-TB treatment (treatment-initiation-delay) was 10 days with an IQR of 4-21days. This is remarkably lower than the treatment-initiation-delay of 72 and 93 days for decentralised and centralised settings respectively documented previously in a South African study (35). This finding is critical to help limit the spread of MDR-TB in the population, by setting up appropriate follow-up strategies from the point of diagnosis to start of treatment. Among the 83.3% of patients confirmed to be on ART during treatment of MDR-TB, 47.9% of them were on ART prior to MDR-TB treatment, while 35.4% were on ART after commencing MDR-TB treatment.

The overall proportion of patients who died was 22.7% similar to the proportion of mortality reported in previous South African studies (16) and is comparable to 17% reported in India (38), but substantially different from 57% noted by Palacios E et al. in Peru (36). The overall proportion of successful treatment was 46.4% akin to that noted in South Africa (16-18) and 48% noted in India (38), but lower than the 61.9% in Lesotho (20). The percentage of cure which was 29.8% was comparable to the 21% documented in Peru (36). Patients who failed treatment made up 2.9% of the entire cohort**,** lower than the 5-8% documented in a meta-analysis by Johnston JC et al. (31) and over the 9% by other studies (16, 38). In this study, a high proportion of default (22.3%) was noted and it is comparable to previous South African

studies (16) and to the 26% noted in India (38). Restricting the analysis to those who died and were on ART before or after commencement of MDR-TB treatment, the proportion of mortality (21.8% vs. 15.4%) was higher for those on ART prior to MDR-TB treatment initiation.

Predictors of mortality, cure and failure were determined during multivariable analyses adjusting for all potential confounders. The following factors were significantly associated with mortality: the use of ART prior to commencement of MDR-TB treatment, being severely underweight and underweight, cavitary lesions on baseline chest x-rays, the presence of other opportunistic infections and other co-morbidities. For predictors of cure, there was a significant interaction term between timing of ART and gender. Factors that positively predicted cure were male patients on ART prior to commencement of MDR-TB, patients aged 46years and older, and patients with CD4 counts between "150-349" and" ≥350" cells/mm³. Negative predictors of cure included: males on ART after commencement of MDR-TB treatment, presence of cavitary lesions on baseline chest x-rays, and modified individualised regimen at baseline. Significant risk factors for failure included: severe anaemia (haemoglobin level <7g/dl) and modified individualised regimen at baseline.

4.2 Systematic overview of the study findings

4.2.1 Predictors of mortality

ART use prior to MDR-TB treatment initiation was significantly associated with higher odds of mortality compared with ART initiation after commencement of MDR-TB treatment. This finding has not been reported before by other studies. Based on this data, a greater percentage of patients who commenced ART before MDR-TB treatment initiation were severely underweight (15.4%). They also had more extra-pulmonary TB (20.7%), adverse events (45.2%), and modified regimen based on patients' history at baseline (31.5%) compared with

patients who started ART after initiation of MDR-TB treatment. This is surprising as it should be assumed that patients should have benefited from being on ARVs before MDR-TB treatment. On the other hand, if this protective benefit of ARVs was in effect, these patients should not have developed MDR-TB in the first instance. It is likely that poor adherence from drug side effects leading to problems of drug resistance and virological failure may have been responsible for this trend.

This result poses questions on the issue of adherence to ART for patients who were already on ART prior to MDR-TB treatment in a country like South Africa with majority of her HIV positive patients on ARVs. Additionally, overlapping drug toxicities from the MDR-TB and ARVs pills may have resulted in the high mortality in this study. There was less likelihood of mortality in patients on ART post MDR-TB treatment initiation, even though more patients on ART after commencement of MDR-TB treatment had other non-TB opportunistic infections (26.6% vs. 42.9%). This could be due to the fact that on starting ARVs there was improved immune reconstitution coupled with the tight adherence counselling, close monitoring and management of adverse events at Sizwe Hospital; hence resultant decrease in mortality.

This study found that being severely underweight and underweight were risk factors of mortality, and demonstrated a biologic gradient with patients who were severely underweight having a higher likelihood of mortality (OR: 3.46) compared with those who were underweight (OR: 2.31). These findings are similar to previous studies (16, 20, 31, 36, 41, 42). In this cohort, 43.5% of the patients were severely underweight and underweight. HIV and TB are linked to malnutrition (41) and wasting syndrome is a hallmark of severity of TB and HIV infection, therefore its strong association as a predictor of mortality irrespective of patients' ART status.

Analysis revealed that the presence of cavitary lesions on chest x-ray at baseline was a risk factor of mortality. There have been conflicting studies on the role of cavitation on chest x-ray as a risk factor of poor outcomes. Some studies have linked the presence of cavitation on chest with longer culture conversion time; a surrogate marker for poor outcomes (43-45), while others have found no statistically significant relationship between cavitation and poor outcomes (31, 46). In a recent study done by Brust JC et al. in South Africa, its failure of finding a significant relationship between cavitation and longer time to sputum conversion may have been due to the limited sample size of 56 patients (46).

The presence of other non-TB opportunistic infections was a significant factor that consistently predicted mortality both in univariable and multivariable analyses. This finding has not been reported before by other studies beyond the descriptive level (36). There is a higher risk of mortality and development of other opportunistic infections in HIV-TB co-infected patients (50, 51). The role of other non-TB opportunistic infections is important in the clinical and prognostic staging of HIV positive patients. Serious opportunistic infections like Kaposi sarcoma, cervical cancer, CMV infections, HIVAN, etc. are already an indicator of the depressed immunity with an increase likelihood of mortality masking the importance of timing of ART initiation in these patients.

In this study the presence of co-morbidities as listed in the methods section was a significant risk factor of mortality. This result was also noticed in a recent study in the United Kingdom (47). There is an established “bidirectional synergistic” relationship between TB HIV co-infection and development of co-morbidities like DM (52-54). Treatment of HIV with ART especially with the protease inhibitors is associated with hyperglycaemia, insulin resistance, dyslipidaemia (55); not only leading to the development and complication of DM, but cardio-vascular, cerebro-vascular, hepatic and renal problems. Most studies done on the role of certain co-morbidities on TB mortality focus on single disease entity like DM; with positive

(56) and negative (31) results. This study is the first in South Africa to in-corporate the presence of other non-communicable co-morbidities apart from DM to assess its impact on mortality in MDR-TB HIV co-infected patients, especially with the emerging link of infectious and non-communicable diseases.

4.2.2 Predictors of cure

Based on this data, male patients on ART prior to initiation of MDR-TB treatment were more likely to be cured compared with female patients commenced on ART after initiating MDR-TB treatment. The interaction between timing of ART and gender was significant nonetheless, neither of each factor (timing of ART nor gender) was significantly associated with cure. While exploring this relationship, it was noticed that the log-odds (hence the likelihood) of cure in females who started ART prior to MDR-TB treatment decreased rapidly by 1.08 times compared with those initiated on ART after commencement of MDR-TB treatment. Among male patients started on ART before MDR-TB treatment, there was an increase in the log-odds by 0.55 times compared with males on ART after commencement of MDR-TB treatment. The reason for this finding is unclear and surprising. Male gender has been associated with poor successful TB outcome (31, 39, 57), compared with female gender. But in these studies timing of ART initiation was not considered.

There have been contradicting evidence on the effect of gender on ART adherence, but in an extensive literature review to determine the existence of gender differences on non-adherence over an 11 year period in developed countries, female gender predicted poor adherence to ART (58). More so, in our study females were younger than males; with 53.2% (494) of females in age group 18-45 years compared with 63.2% of males in age group 46-76 years and more females 51.6% were on ART prior to commencement of MDR-TB treatment compared with males. Older adults have been shown to have better adherence compared with

younger adults (59-61). The age differentials may have impacted on gender of patients modifying the relationship between timing of ART and cure.

Reduced adherence to ART in females have also been linked to depressive symptoms (62, 63) and lack of supportive interpersonal relationships (64). A study done in South Africa showed that about 70% of the MDR-TB households were headed by females (65) who are faced not only with the challenges of life-long effects of HIV and ART coupled with the long term treatment duration and follow-up required for MDR-TB but also with the arduous task of child-bearing and rearing. These huge responsibilities may have poorly affected the adherence of females who were on ART prior to commencement of MDR-TB treatment as such the overall effect on cure.

The data revealed that patients aged 46 years and older had a higher odds of cure compared with those from the younger age group. About 18.2% of the cohort were adults aged 46 years and older. In a study by Chan ED et al., older adults on fluoroquinolone therapy had higher likelihood of successful treatment (66). There is a correlation between increasing age and positive adherence to ART, especially for adults' ≥50 years of age (59-61). This finding may have positively affected adherence to anti-TB medications; hence a higher likelihood of cure in these group of patients.

Patients with CD4 cell counts in the group of "150-349" and "≥350" cells/mm³ were significantly more likely to be cured compared with patients with CD4 "<150" cells /mm³. In this cohort, 35% and 17% of patients were in the above significant CD4 categories respectively. The relationship between increasing CD4 and cure has not been reported by others, even though CD4 count <200 cells/mm³ has been shown to be a predictor of unsuccessful outcomes in MDR-TB (40) and in XDR-TB patients (67). Thus with early HIV diagnosis, timely commencement of ARVs and maintenance of strict adherence, it should be

anticipated that an increase CD4 count and invariably improved immunity and virological suppression will result in improved favourable treatment outcomes.

This research also established that patients with cavitation on chest x-ray at baseline were less likely to be cured compared with those without cavitary lesions. Cavitation on chest x-rays are particularly seen in HIV co-infected patients with higher CD4 count of ≥200 cells/mm³ (68), and is indicative of high bacillary load (69) and likelihood of smear positivity (70). This result is consistent with other studies (43-45) establishing the association between cavitation, longer time to sputum conversion and hence decrease likelihood of cure and inevitably poor successful outcome. Additionally in this study cavitary lesions also predicted higher odds of mortality, which further strengthens its relationship with unsuccessful outcomes.

The study found that patients with modified individualised regimen at baseline were less likely to be cured compared with patients on standardised regimen. Contrary to this findings, most studies have found individualised regimen compared with standardised regimen to be associated with successful outcome (30, 41), though the meta-analysis findings by Orenstein EW et al. did not detect a statistically significant difference between the two groups. This disparity is not surprising because in our context, treatments were modified at baseline based on existing co-morbidities, adverse events and extensive resistance pattern including pre-XDR strains, but not based on DST results only. In view of this fact, modifying treatment may have impacted on the time to culture conversion and hence the proportion of patients cured.

4.2.3 Predictors of failure

Severe anaemia (haemoglobin <7.0mg/dl) at baseline was a predictor of treatment failure during the multivariable analysis. The cause of anaemia in MDR-TB HIV co-infected patients are multi-factorial, resulting from the HIV/mycobacterial infection and treatment

with both anti-TB and ARV medications. This finding is consistent with that of Mitnick C, et al. where low haematocrit was associated with about 4 times increase in the hazard of failure or death compared with normal haematocrit (41). This result is important because it will act as a reminder to physicians in the management of TB/HIV co-infected patients by encouraging balanced nutrition and optimization of haemoglobin levels while on treatment.

Modified individualised regimen at baseline for patients based on co-morbidities and adverse-events was significantly associated with treatment failure. For these patients some drugs were delayed at baseline pending improvement in clinical condition. This supports the result by Leimane V et al. which noticed that patients on ≤ 5 drugs for 3 months or more were more likely to fail or die (42). This is analogous to the results seen during the multivariable analysis for predictors of cure, where patients on individualised regimen at baseline had a lower likelihood of cure. Even though this study revealed a marginally significant relationship between cavitation on chest x-ray ($p = 0.08$) and the presence of co-morbidity ($p = 0.07$) with treatment failure, there was a significant association between these factors and mortality. This further supports the plausibility of these factors being responsible for poor outcomes.

4.3 Potential study biases

4.3.1 Collection of exposure and outcome data

Self-report of ART status by some of the patients who started ART before commencement of MDR-TB treatment would have presented a likelihood of information bias; but ART status of individuals were confirmed on referral letters or telephonically by contacting referral clinics where patients were initiated on ART and by inspection of pills. Observer bias was minimised during data collection by first ascertaining the outcome before determining the ART status of the patient. Instrument bias may have occurred while measuring some of the

clinical exposure variables like height, weight, etc. Nevertheless, repeat measurement of other exposure variables, like CD4, haemoglobin, etc., and ascertainment of HIV status by the NHLS where results were discrepant helped to minimise misclassification of patients based on the exposure variables.

Selection bias was minimised by including only confirmed HIV positive adults and also excluding patients not on ART and those with unavailable ART status during MDR-TB treatment. Patients who started ART after completing MDR-TB treatments were not included as exposed to ART during treatment to avoid over-estimation of the effect of ART use after initiating MDR-TB treatment on the outcomes. Patients with mono/poly resistance were also excluded as these were not truly MDR-TB cases. Outcomes were objectively measured, avoiding misclassification bias as majority of patients were confirmed cured or failed treatment based on DST from NHLS and extensive follow-up. Mortality was also confirmed in the hospital and for patients who died at home, regular tracing and reminders for visits helped in ascertaining home-related mortality.

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

Exposure variables were correctly stratified and univariable analyses were done and factors at a $p < 0.1$ were considered covariates for inclusion in the multivariable models which adjusted for several factors to limit residual confounding. Factors at $p < 0.05$ were considered as significant predictors of mortality, failure or cure. As such, the strength of association between the main exposure variable, other covariates and each outcome may not have been due to chance.

This study depended on already collected data from medical records, hence may not have measured all the possible confounders. Viral load for patients would have been a true test of adherence especially for patients on ART prior to initiating MDR-TB treatment, thereby

helping in the explanation of the relevant findings. However, viral load could not be used as the definition of virological suppression varied over the years according to the NHLS definitions and also few data were collected for this variable. Baseline data on height were not collected completely especially for the first two years of the study, resulting in missing variables for BMI of about 19% of cases. Dates for ART initiation were not completely documented for most patients who started ART before commencement of MDR-TB treatment, hence imputation of complete data was done to help ascertain the duration for which patients were on ART. Data on occupation of the patients were limited to employed or un-employed and this did not allow for risk assessment of certain occupations on MDR-TB.

4.4 Study limitations

In this study, timing of ART was stratified as before or after commencement of MDR-TB treatment and this may not allow proper assessment of the effect of duration of ART on the outcomes. Some patients may have been on ART long before MDR-TB treatment initiation, while others may have commenced ART just before the start of MDR-TB treatment. Information on baseline ART regimen were not collected, as this would have been a pointer to drug resistance and virological failure and could have possibly helped in explaining the role of timing of ART on mortality and cure.

Some of the data on other opportunistic infections, co-morbidity, adverse events, height, and weight were not documented in the case notes, hence assumed to be missing. This may have affected the statistical power to detect such variables as significant predictors during the multivariable analyses. Coding co-morbidities as a yes or no variable instead of looking at individual diseases may have overestimated the effect of such on the outcomes in patients who had one or two co-morbidities compared to those who had a combination of highly fatal co-morbidities.

Different guidelines were used through the years for initiation of ART in MDR-TB treatment (prior to 2010, CD4 of <350 cells/mm^3; while in 2010 compulsory initiation as soon as patient can tolerate ART irrespective of the CD4 count). This may have affected the outcomes over the years, with poorer outcomes before the present policy was effectively put to practice. Also change of MDR-TB regimen from ofloxacin to moxifloxacin, with all patients not subjected to the same drugs over time may have affected the outcomes too. Using baseline clinical variables like CD4, haemoglobin, and even weight which are known to be time varying as predictors of the 3 major outcomes, may not give a true picture of the association with the outcome (as these covariates may decrease or increase over time).

Using cure alone without merging with "treatment completed" may have resulted in under-estimation of the total proportion of the patients cured. There might have been a higher percentage of cure, but most patients do not send back their follow-up DST results to Sizwe (lost to follow-up after completing treatment) and these may have been missed. However, the strength with using cure only is that these patients were actually confirmed cured through micro-biologic results and extensive follow-up over a period of time.

Data on cause-specific mortality were not collected. Some patients may have died due to the presence of other co-morbidities and opportunistic infections other than MDR-TB. The quality of data collected at Sizwe improved over the years, however, information were poorly recorded in the early years (2007/2008).

4.5 Study strengths

The study used retrospectively collected data on exposure variables which preceded the outcomes of MDR-TB, hence credible in temporality. Patients initiated on ART at Sizwe Hospital had definite start dates and so were not likely to be misclassified as those who started ART prior to commencement of MDR-TB treatment. It is also a standard practice at

Sizwe Hospital for physicians to ascertain the ART status of patients at baseline, reducing the likelihood of misclassification bias in the exposure groups. Good follow-up on ART treatment via repeated adherence counselling and drug monitoring were done once patients commenced MDR-TB treatment at Sizwe hospital and adverse events were monitored, documented and treated by managing physicians.

This study reported final outcomes of MDR-TB among a cohort of HIV positive patients after at least a two year follow-up period hence unlikely to under-estimate the outcomes. This is one of the largest cohort of MDR-TB HIV co-infected patients, allowing reasonable power to detect a difference between the two exposure groups in relation to the major outcomes and other risk factors for mortality, cure and failure. Certain variables like weight, height, CD4 count, haemoglobin, and chest x-rays were collected within specified periods to prevent disparate exposure duration hence, preventing over or under-estimation of the effect size. Information on certain exposures like other opportunistic infections, co-morbidity and adverse events were collected and this may have helped to explain the predictors of mortality, cure and failure.

4.6 Generalizability

South Africa is among one of the countries with very wide ART coverage, hence these results should be interpreted with caution as they may not be generalizable to regions with low ART coverage. This study was done in Gauteng province and findings may not be generalizable to other provinces as MDR-TB/HIV co-infection prevalence may be different for different provinces.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

In conclusion, outcomes of MDR-TB did not differ significantly between the two ART groups except for mortality which was significantly higher among those who started ART before commencement of MDR-TB treatment. Factors predicting high mortality included the use of ART before commencement of MDR-TB treatment, being severely underweight and underweight, cavitary lesions on baseline chest x-ray, the presence of other opportunistic infections, and other co-morbidities. Gender significantly modified the relationship between timing of ART initiation and cure. Positive predictors of cure included males on ART prior to commencement of MDR-TB treatment, patients aged 46 years and older, and those with CD4 count between "150-349" and ≥350 cells/mm³. Factors negatively predicting cure included: cavitary lesions on baseline chest x-rays, and modified individualised regimen at baseline. Risk factors of treatment failure included: severe anaemia and modified individualised regimen at baseline.

5.2 Recommendations

In summary, the study findings of predictors of mortality, cure and failure in MDR-TB HIV co-infected patients as outlined above are valid and unlikely to be due to chance, sampling bias or residual confounding. This work is unique as it provides new information while also reinforcing old knowledge to clinicians and public health practitioners for the identification of TB populations at higher risk of death, treatment failure and decreased cure.

The lower MDR-TB treatment-initiation-delay of 10 days at a centralised facility like Sizwe Hospital highlights that interventions put in place for strict follow-up and early initiation of MDR-TB treatment is effective and highly commendable. Strides at shortening this time

further is necessary, in order to continually reduce the spread of drug resistant MTB in the population.

Findings supportive of high mortality in patients who were already on ART before commencement of MDR-TB treatment raise concerns on general ART adherence and monitoring at different HIV clinics across Gauteng Province, which should be re-visited. Strict adherence to ART in HIV positive patients irrespective of their TB status is needful to prevent further deterioration in their immune status and development of MDR-TB and other severe opportunistic infections.

Clinicians should not undervalue the role of adherence to ART treatment in patients who are already on ART before commencement of MDR-TB treatment. Appropriate management of already existing adverse events, opportunistic infections and co-morbidities in these patients is important to maximise the benefits of being on ART before commencement of MDR-TB treatment, and on the whole achieve better treatment outcomes.

The study results also places an emphasis on the role of Public health practitioners to intensify gender and age-specific intervention programmes (behavioural and biological) targeted at increasing adherence and drug monitoring for HIV infected patients (especially among females and younger adults).

This work also confirms that timely (early) initiation of ART in MDR-TB patients, strict adherence counselling and treatment monitoring, early diagnosis and management of adverse events and other co-morbidities would decrease mortality, resulting in better treatment outcomes (20, 36, 48).

In a broader perspective, the findings of this study calls for governmental, non-governmental, inter-sectorial and public health collaborations in providing appropriate health funding for

public health policies on preventive and other intervention programmes to lower the risk factors for mortality, poor successful treatment and failure in this vulnerable population.

5.3 Suggestions for further studies

Based on the above findings, further research should be done using biologic parameters like baseline virological suppression for patients on ART prior to commencement of MDR-TB treatment to assess their adherence level to ART, and comparing treatment outcomes with those that started ART after MDR-TB treatment initiation to assess if this has a role in the increase risk of mortality in these group of patients.

Another important areas for research include the need to understand clearly the reason why males who were on ART prior to MDR-TB treatment were more likely to be cured, compared with females and assessment of behavioural and biologic factors that impact negatively on ART adherence in females.

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APPENDICES/ ANNEXURES

Appendix 1: Ethics Clearance Certificate.

R14/49 Dr Umanah Teye Aniefiok

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130961

NAME: (Principal Investigator)	Dr Umanah Teye Aniefiok
DEPARTMENT:	Public Health Infectious Disease Epidemiology Sizwe Tropical Disease Hospital
PROJECT TITLE:	Effects of Timing of Antiretroviral Therapy Initiation on Multidrug-Resistant Tuberculosis Outcomes in Human Immunodeficiency Patients in Sizwe Tropical Disease Hospital, Johannesburg South Africa, 2007-2010
DATE CONSIDERED:	27/09/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Peter Nyasulu
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/10/2013

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 18th October, 2013.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Change of title approval by Faculty of Health Sciences, University of the Witwatersrand.

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172040

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

07 January 2014
Person No: 607185
TAA

Dr TA Umanah
14 Willem Coetzer Street
Ermelo 2350
Mpumalanga
0000
South Africa

Dear Dr Umanah

Master of Science in Epidemiology: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Science in Epidemiology** has been approved:

From:

To: **Effects of timing of anti-retroviral therapy initiation on multi drug-resistant tubercolosis outcomes in HIV co-infected patients in Sizwe Tropical Disease Hospital, Johannesburg, South Africa, 2007-2010.**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3: Approval to review medical records at Sizwe Tropical Disease Hospital, Johannesburg.

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Enq. : Dr. M. C. Louw
☎ : (011) 531.4305
Fax : (011) 531.4377
Date : 02 September 2013

Att: Dr. Teye Umanah

RE: EFFECTS OF TIMING OF ANTIRETROVIRAL THERAPY INITIATION ON MULTIDRUG-RESISTANT TUBERCULOSIS OUTCOMES IN HIV CO-INFECTED PATIENTS IN SIZWE TROPICAL DISEASE HOSPITAL JOHANNESBURG, SOUTH AFRICA, 2007 - 2010.

Your request to conduct the above study in Sizwe Tropical Disease Hospital is acknowledged. Support for the study to be conducted is hereby granted.

Yours sincerely

Dr. M.C. Louw
CEO: Sizwe Tropical Disease Hospital

GAUTENG HEALTH DEPARTMENT
Sizwe Tropical Disease Hospital
Private Bag X2
Sandringham
2131

DR. M. C. LOUW
Chief Ececutive Officer
Date: 02/09/2013

Appendix 4

Table 3.2.1: Bivariate analysis of demographic characteristics of MDR-TB HIV co-infected adults based on exposure to ART before or after commencement of MDR-TB treatment.

Factors	ART prior to commencement of MDR-TB treatment N (%) (N = 545)	ART after commencement of MDR-TB treatment N (%) (N = 402)	Test Statistic	p-value
Age	36 (31-43)*	35.5 (31-42)*	z = -0.587	0.557
Age groups				
18-45	448 (82.2)	334 (83.1)	chi = 0.125	0.723
46-76	97 (17.8)	68 (16.9)		
Gender				
Male	264 (48.4)	193 (48.0)	chi = 0.017	0.896
Female	281 (51.6)	209 (52.0)		
District				
Westrand	58 (10.6)	54 (13.4)	Fisher's Exact	0.585
Sedibeng	39 (7.2)	30 (7.5)		
Tswhane	102 (18.7)	79 (19.7)		
Ekhurhuleni	124 (22.8)	95 (23.6)		
City of Johannesburg	216 (39.6)	142 (35.3)		
Metsweding	6 (1.1)	2 (0.5)		
Race				
Other	6 (1.1)	7 (1.7)	Chi = 0.701	0.403
Black	539 (98.9)	395 (98.3)		
Employment status				
Employed	149 (27.3)	109 (27.1)	Chi = 0.006	0.939
Unemployed	396 (72.7)	293 (72.9)		

N- Total number in each group; % - Column percentages;
*Median and Inter-quartile range (IQR);
Test statistic based on chi-square, Fisher's Exact and Wilcoxon Rank-sum tests.

Appendix 5

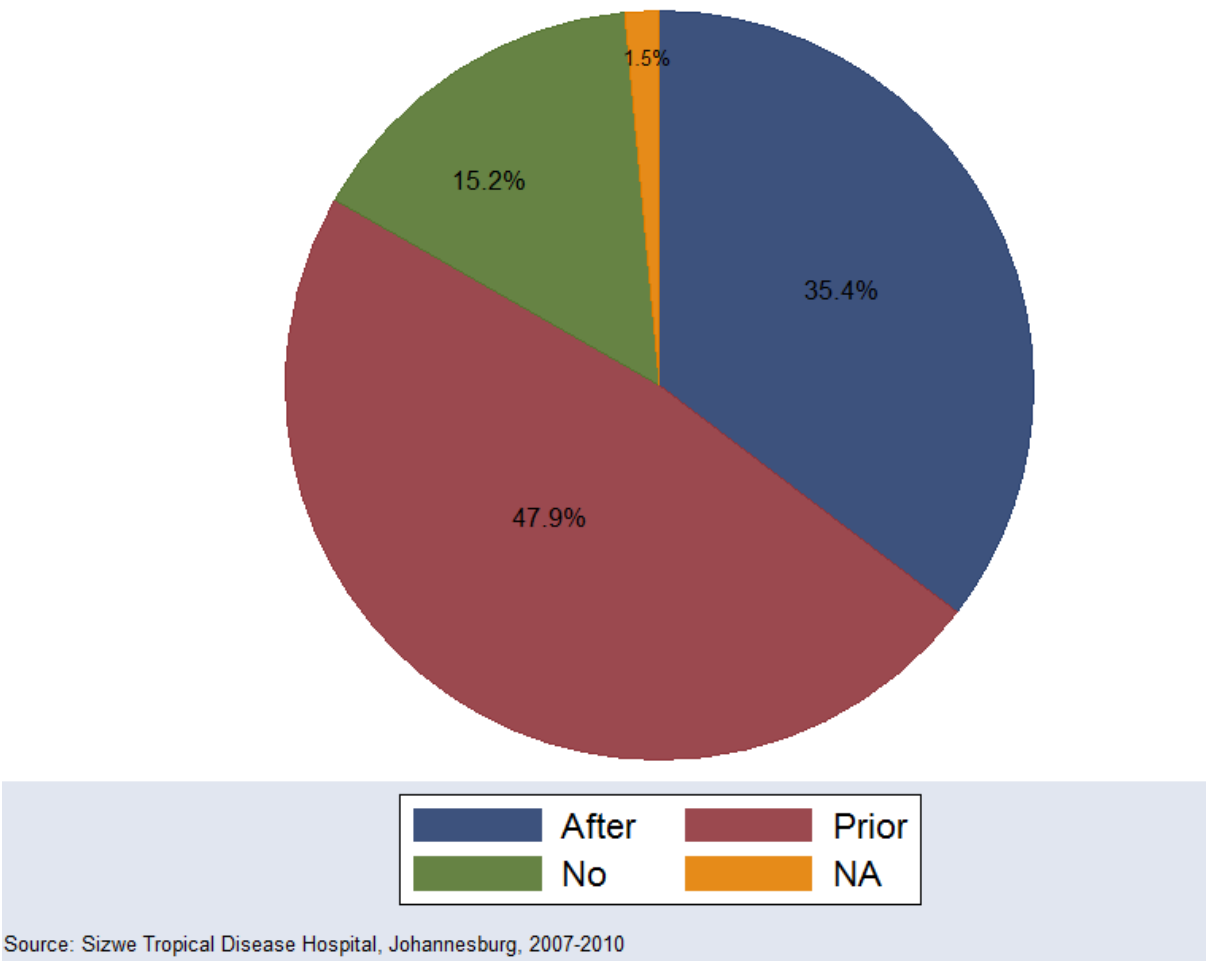


Figure 3.3: *ART status of patients on treatment for MDR-TB at Sizwe Tropical Disease Hospital, Johannesburg from 1st January, 2007 to 31st December, 2010. "No"- Not on ART, "NA"- ART information not available, "After"- Initiated on ART after commencement of MDR-TB treatment, "Prior"- Initiated on ART before commencement of MDR-TB treatment.*

Appendix 6

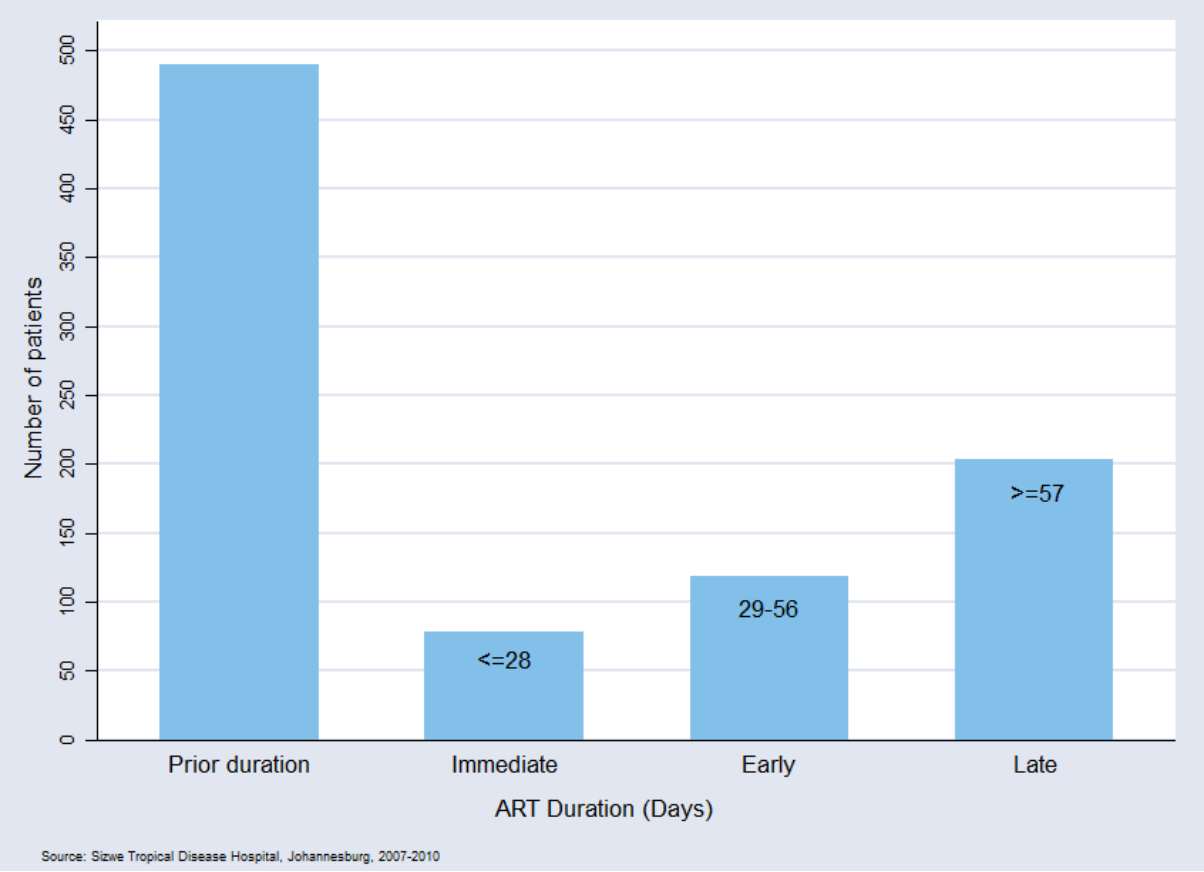


Figure 3.4: *Duration on ART treatment in HIV positive MDR-TB patients at Sizwe Tropical Disease Hospital, Johannesburg.*

Appendix 7

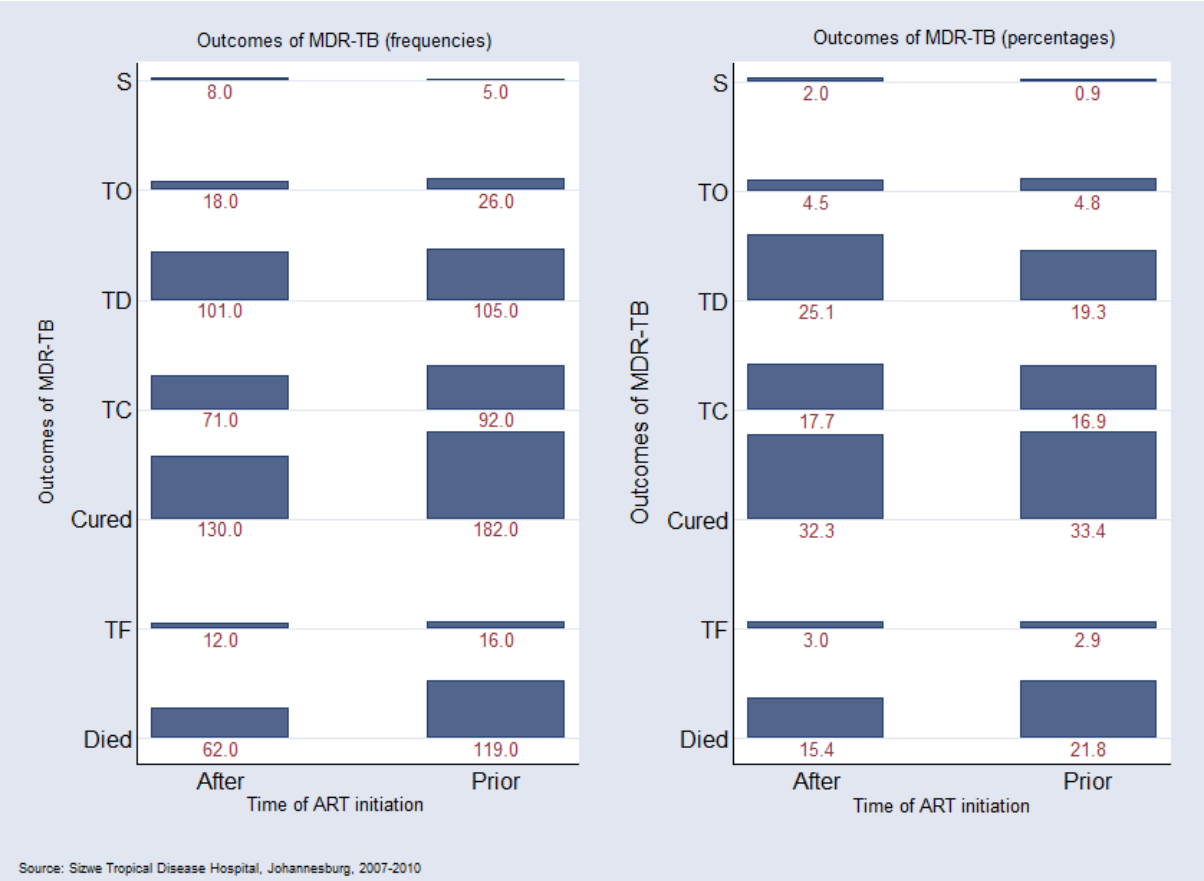


Figure 3.5 *Tab-plots of MDR-TB outcomes by timing of ART initiation showing frequency and proportion of patients in each outcome category. S "Still on treatment"; TO "Transferred-out"; TD "Treatment Defaulted"; TC "Treatment Completed"; and TF "Treatment Failure".*

Appendix 8

Table 3.6.1: Predicted log-odds of the interaction term between timing of ART initiation and gender

.predict logitmfit, xb

. table artreg_new gender, c(mean logitmfit)

Time of ART initiation	Gender	
	Male	Female
After	-1.129898	-.3676776
Prior	-.5102376	-.7653566

The log-odds (hence the likelihood) of cure decreases more rapidly in females on ART prior by -1.08times compared to females on ART after commencement of MDR-TB treatment. For males, the log-odds of cure increases by 0.55times in those who were on ART prior compared to males on ART after commencement of MDR-TB treatment.

Table 6.2: *Predicted probabilities of the interaction term between timing of ART initiation and gender*

.predict mfit, pr

.table artreg_new gender, c(mean mfit)

Time of ART initiation	Gender	
	Male	Female
After	.2556391	.4135338
Prior	.3837838	.327957