MICROBIOLOGICAL PARAMETERS THAT INFLUENCE THE TREATMENT OUTCOMES OF MONODRUG AND MULTIDRUG-RESISTANT TUBERCULOSIS

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Microbiological parameters that influence the treatment outcomes of monodrug and multidrug-resistant tuberculosis

Keywords

Age
Antiretroviral agents
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Sputum culture
Sputum conversion
Sputum reconversion
Treatment outcomes

ABSTRACT

MICROBIOLOGICAL PARAMETERS THAT INFLUENCE THE TREATMENT OUTCOMES OF MONODRUG AND MULTIDRUG-RESISTANT TUBERCULOSIS

Background and purpose of the study

Previous studies have reported microbiological parameters such as HIV infection, resistance to anti-TB drugs such as fluoroquinolones, resistance to previous treatment with anti-TB drugsand extrapulmonary TB, causing poor treatment outcomes in patients with monodrug and multidrug-resistant tuberculosis. However, little is known about the time to sputum culture conversion in HIV-positive patients infected with monodrug and multidrug-resistant tuberculosis in South Africa, and currently there is no information on the effects of inappropriate (i.e. low and high) anti-tuberculosis drug-dose on the time to sputum culture conversion in monodrug and multidrug-resistant TB patients. The aim of the study was to investigate whether or not there is a difference between the time to sputum culture conversion in drug-resistant tuberculosis patients with HIV, and those without HIV infection. It also aimed to find out whether inappropriate (i.e. low and high) anti-tuberculosis drug dose could affect the time to sputum culture conversion in drug-resistant TB patients. In addition, the influence of HIV infection (CD4 count and viral load), drug resistance type, impact of antiretroviral duration before TB treatment, the replacement of ofloxacin by moxifloxacin and DR-TB localization were assessed on drug-resistant TB treatment outcomes.

Methods

This study was designed as a retrospective observational study that assessed the influence of microbiological parameters on DR-TB treatment outcomes. The study involved patients admitted for treatment of drug-resistant TB between 1 January 2009 and 31 December 2015 at Brewelskoof Hospital, South Africa. The study population includes male and female patients, HIV-positive and HIV-negative, 18 to 65 years old, with confirmed MDR-TB and mono-resistance TB (RMR-TB and HMR-TB). Sputum culture results were recorded monthly. Sputum culture conversion was defined as two negative cultures taken at least one month apart. Time-to-sputum culture conversion was measured from the day of initiation of DR-TB therapy. The

influence of sputum culture conversion by HIV status and the influence of inappropriate anti-TB drug dose on the time to sputum culture conversion was assessed using the ICLIFETEST procedure (IC indicates interval censoring). The Kruskal-Wallis one way analysis of variance was used to correlate the duration of antiretroviral therapy before TB treatment and the CD4 counts as well as viral load parameter at baseline and at the end of treatment on the treatment outcomes in DR-TB patients. The chi-square test was used for the other variables.

Results

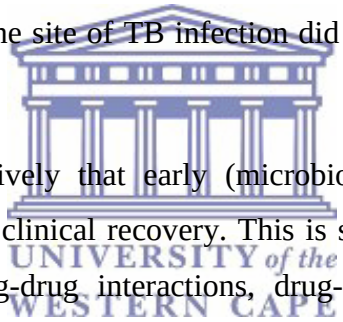
Of 244 MDR-TB patients, 229 (93.9%) patients converted within the first six months of treatment and there was no difference in the proportion that converted based on HIV status. Median time for conversion was 36 days (IQR 24-72) in HIV-positive patients and 40 days (IQR 26-72) in HIV-negative patients.Of 103 RMR-TB patients, 102 (99.3%) converted within the first 6 months of treatment and there was no difference in the proportion that converted based on HIV status. Median time for conversion was 26.5 days (IQR 16.5- 46) in HIV-positive patients and 34 days (IQR 21-55) in HIV-negative patients with RMR-TB. Out of 39 HMR-TB patients, 30 (76.9%) converted within the first 6 months of treatment and there was no difference between HIV-positive and HIV-negative patients. Median time for conversion was 69 days (IQR 57-103) in HIV-positive patients and 48 days (28-103) in HIV-negative patients with HMR-TB.

Although there was no statistically significant difference in the time to sputum culture conversion in HIV- positive and HIV- negative patients with monodrug and MDR-TB, treatment outcomes were statistically significantly worse for HIV-positive patients with MDR-TB. Inappropriate (i.e. low or high) anti-TB drug dose did not influence the time to sputum culture conversion. We observed that there was no statistical significant difference between drug-resistant TB patients who received either of the inappropriate (i.e. low or high) anti-TB drug dose. There were no statistically significant differences between MDR-TB, RMR-TB, and HMR-TB treatment outcomes with regard to the other microbiological parameters investigated in this study.

Conclusion and recommendations

In this study, we were able to determine the time to sputum culture conversion in DR-TB patients. There is was no difference between the sputum culture conversion time in HIV-positive patients and HIV-negative patients with MDR-TB, RMR-TB, and HMR-TB respectively. There was limited evidence to suggest that inappropriate (i.e. low and high) anti-TB drug dose affects the time to sputum culture conversion in MDR-TB, RMR-TB, and HMR-TB patients. Although, from the survival analysis, there was no significant difference between drug-resistant TB patients who received any inappropriate (i.e. low and high) anti-TB drug dose as compared to drug-resistant TB patients who did not receive any inappropriate anti-TB drug dose.

We were not able to assess if changes in CD4 counts and viral load affect the treatment outcomes in HIV-positive patients with DR-TB due to limited data, hence this objective was not achieved. The duration of antiretroviral therapy, the type of anti-TB drug resistance, the replacement of ofloxacin with moxifloxacin and the site of TB infection did not have any influence on DR-TB treatment outcomes.



Our findings established conclusively that early (microbiological outcome) sputum culture conversion does not suggest early clinical recovery. This is suggestive of involvement of other factors, e.g pharmacokinetic drug-drug interactions, drug-food interactions or drug-disease interactions that may influence the treatment outcomes in drug-resistant TB patients.

We had an unequal distribution of patients with regard to CD4 counts and viral load, with imbalance in the different categories of mono-resistance TB cases and DR-TB localization. We recommend further studies with a higher sample size of patients to address the unequal distribution with regard to CD4 counts and viral load. Further research with larger sample size should be done in order to confirm and extend the understanding of HIV infection, and inappropriate anti-TB drug dose on the time to sputum culture conversion in MDR-TB, RMR-TB and HMR-TB patients. The clinical impact of sputum culture conversion time, inappropriate anti-TB drug dose, extrapulmonary TB, drug resistance TB type, the replacement of ofloxacin with moxifloxacin, and antiretroviral history on the treatment outcomes in MDR-TB, RMR-TB, and HMR-TB are still largely unexplored, and further research with a larger sample size should

be done in order to establish which microbiological parameters may contribute to poor treatment outcomes in these patients, and whether or not these microbiological parameters are increasing the risk of treatment failure or other poor clinical outcomes.

April 2017

DECLARATION

I declare that this thesis on the microbiological parameters that influence the treatment outcomes of monodrug and multidrug-resistant tuberculosis is my work, that it has not been submitted before for any degree or examination at any other university, and that all the sources I have used or quoted have been indicated and acknowledged by means of complete references.

Christabel Osaretin Okonji April 2017

Signed: UWC/ Bellville

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ABBREVIATIONS AND ACRONYMS

ADR	Adverse reaction
AFB	Acid fast bacilli
AIDS	Acquired immune deficiency syndrome
ALT	Alanine amino transaminase
ART	Antiretroviral therapy
ARV	Antiretroviral
ARVs	Antiretroviral drugs
AUC	Area under the curve
AZT	Zidovudine
BH	Brewelskoof Hospital
BMI	Body mass index
CDC	Center for disease control and prevention
CD4	Cluster difference 4
CFR	Cumulative fraction response
CL	Clearance
CNS	Central nervous system
CTX	Co-trimoxazole
CPT	Co-trimoxazole preventative therapy
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DOH	Department of health
DOTS	Direct observed treatment short course
DR-TB	Drug resistance-Tuberculosis
DST	Drug susceptibility testing
EMB	Ethambutol
EFV	Efavirenz
ESR	Erythrocytes sedimentation rate
ETH	Ethionamide
EPTB	Extra-pulmonary tuberculosis

fAUC	Area under the curve of the free plasma concentrations
FDA	Food and drug administration (United States)
FQN	Fluoroquinolones
GFR	Glomerular filtration rate
H	Haarlem
h	Hour
HAART	Highly Active Anti-retroviral Therapy
HIV	Human Immunodeficiency Virus
HMR-TB	Isoniazid mono-resistant TB
IM	Intramuscular (injection)
INH	Isoniazid
IRIS	Immune reconstitution inflammatory syndrome
IPT	Isoniazid Preventive Therapy
IV	Intravenous (injection)
Kg	Kilogram
L	Litre
LJ	Lowenstein Jensen
MBGT	*Mycobacterium* Beijing Genotype
MCS	Microscopy culture and sensitivity
MDR	Multidrug resistant
MDR-TB	Multidrug resistant tuberculosis
MIC	Minimum inhibitory concentration
mg	milligram
MTB	*Mycobacterium tuberculosis*
MDG	Millennium development goal
NDOH	National Department of Health
NHLS	National health laboratory services
NNRTIs	Non- nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
PAS	Para-aminosalicyclic acid
PIs	Protease inhibitors

PK-PD	Pharmacokinetic- pharmacodynamic
PPD	Positive purified derivative
PTA	Probability of target attainment
PTB	Pulmonary tuberculosis
PZA	Pyrazinamide
RIF	Rifampicin
RMR-TB	Rifampicin mono-resistant TB
RNA	Ribonucleic acid
RR-TB	Rifampicin resistant TB
TB	Tuberculosis
TBM	TB Meningitis
TMC207	Bedaquiline
TDM	Therapeutic drug monitoring
3TC	Lamivudine
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis
ZN stain	Ziel-Nielsen staining technique

CHAPTER ONE: INTRODUCTION AND MOTIVATION FOR THE STUDY

1.1 Tuberculosis and human immunodeficiency viral infection: Globally and in South Africa

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and is the most common cause of death among patients infected with the human immunodeficiency virus (HIV). According to the World Health Organization (WHO),in 2015about 10.4 million new TB infections occurred, with 1.4 million people dying of TB and 0.4 million dying of TB and HIV infection (WHO, 2016). The number of TB and HIV infections has decline globally, the only exception is sub-Saharan Africa, which has the greatest burden of TB and HIV infections (WHO, 2016). In this region, 75% of the people co- infected with TB and HIV died in 2015 (WHO, 2016). Despite the progress seen, TB has also been the most common cause of death in South Africa from 2005 to 2014 (SSA, 2015). Tuberculosis and the human immunodeficiency virus (TB/HIV) co-infection is thought to be one of the main constraints to achieving TB control inSouth Africa.

In 2015, South Africa was ranked as having the sixth highest burden of TB worldwide (WHO, 2016), though the country is making progress towards controlling TB, and the 2016 Global Tuberculosis report highlights a declining incidence and prevalence of TB in South Africa (WHO, 2016). The TB situation in South Africa has improved, taking it from the third highest affected country in 2011 to the sixth highest in 2015 (WHO, 2016). The method used to address the challenges associated with the management of drug-susceptible TB in South Africa has been the WHO recommended Directly Observed Treatment Short-course (DOTS) strategy. South Africa adopted the DOTS strategy in 1996, but despite investments in TB control, progress toward reaching programme objectives has been slow (Mukinda et al., 2012). Treatment success rates for drug-susceptible TB have increased from 63% in 2000 to 78% in 2014, although the rate still falls short of the WHO-recommended goal of 85% (WHO, 2016).

1.2 Drug resistant tuberculosis: Globally and in South Africa

Drug resistant tuberculosis (DR-TB) continues to threaten global TB control and is a major health concern in many countries. According to a recent report, South Africa was among the 30 highest drug-resistant tuberculosis-burdened countries in the world (WHO, 2016).The number of persons diagnosed with drug-resistant TB has increased significantly over the last decade from 2000 patients in 2005 to 18,734 in 2014 (WHO, 2015).

Monodrug resistance TB is defined as resistance to one first-line anti-TB drug only (WHO, 2013),and resistance to Isoniazid (INH) is the most common type of mono-resistance among *Mycobacterium tuberculosis* isolates. The prevalence of Isoniazid mono-resistant TB (HMR-TB), which is resistant only to Isoniazid (WHO, 2015), ranges from 4-12% for all TB cases, with a global average of 8.1% for new cases (Hoopes et al., 2009; Villegas et al., 2016; Wang et al., 2014; WHO, 2014).There is less evidence for Rifampicin mono-resistant TB (RMR-TB), which is defined as resistance to Rifampicin alone (WHO, 2015). Rifampicin mono-resistant TB prevalence of under 1% for new TB cases within Europe was reported in 2010, 12% in Lima Peru and 3.2% in Zambia (Mulenga et al., 2010; Sandgren et al., 2012; Villegas et al., 2016).

The increased frequency of Rifampicin mono-resistance has been reported by three South African studies (Dramowski et al., 2012; Mukinda et al., 2012; Coovadia et al., 2013). Mukinda et al (2012) show significantly increasing trends in RMR-TB over a 5-year period (2004–2008). The authors report that during this period RMR-TB cases more than tripled, from 31 cases in 2004 to 98 cases in 2008. Coovadia et al (2013) report that the proportion of RMR-TB varied from a low of 7.3% to a high of 10.0%, with an overall average of 8.8% within a 3-year period (2007-2009). Dramowski et al (2012) also report that RMR-TB disease is increasingly encountered, particularly among HIV-infected and HIV-exposed non-infected children in the Cape Province within a 7-year period (2003 - 2009).

Multidrug resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines (WHO, 2016). MDR-TB is of

increasing concern globally. Among previously treated TB patients, 20% have MDR-TB (WHO, 2015). It is estimated that 3.3% of new TB cases are MDR-TB, globally (WHO, 2015). According to the World Health Organization, 480,000 new cases of MDR-TB and 190,000 related deaths occurred in MDR-TB patients in 2014 (WHO, 2015; WHO, 2016).

The rise of MDR-TB in sub-Saharan Africa is causing great concern and is complicated by HIV infection, thus making the eradication of the drug-resistant bacteria difficult.According to a report by the World Health Organization in 2007, South Africa had the highest number of MDR-TB cases in Africa (WHO, 2009). An increase in MDR-TB was seen in all nine provinces, with the greatest increase in KwaZulu-Natal Province with 11393 (25.2%), followed by the Western Cape Province with 10947 (24.2%) (Department of Health, 2011). Furthermore, KwaZulu- Natal Province has emerged as a global hotspot of drug resistant TB and HIV co- infection, with more than 70% of sufferersco- infected with HIV, and the mortality rate as high as 71% (Visser et al., 2012). In addition, the treatment of MDR-TB remains lengthier and more complex when compared to first-line TB therapy, with a higher pill burden and greater risk of adverse effects from drug toxicity (Satti et al., 2012). Treatment success rates in patients with drug-resistant TB remain unacceptably low 52% (WHO, 2016). The wider use of shorter MDR-TB treatment regimens of 9–12 months, and of new TB drugs (bedaquiline and delamanid) for patients with MDR/XDR-TB, could help to improve this situation (WHO, 2016).

The discovery of the *Mycobacterium tuberculosis* strain, with extensive drug resistance in the Province of KwaZulu-Natal in 2005, alerted global attention, not only to the drug-resistant TB problem in the country, but also to worldwide resistance (Gandhi et al., 2006). Drug resistant TB, especially MDR-TB and XDR-TB,has also emerged as a serious threat to the control of TB in South Africa. The presence of extensivelydrug–resistant tuberculosis (XDR-TB) is of great concern in South Africa. XDR-TB is defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable agent (WHO, 2016). A previous study conducted in KwaZulu-Natal Province in South Africa reported a prevalence of XDR-TB of 6% among patients with TB and a mortality rate exceedingly high (98%) in HIV- infected patients with

XDR-TB (Gandhi et al., 2006).

Recent studies conducted in South Africa within a period of 9 years (2002- 2010) (Dheda et al., 2010) and a period of 5 years (2008- 2012) (Pietersen et al., 2014) have reported poorer treatment outcomes in XDR-TB patients, irrespective of HIV infection. These investigators have reported that long-term treatment outcomes of XDR-TB are poor, irrespective of HIV infection. They reported mortality rates of 50% (Dheda et al., 2010) and 73% (Pietersen et al., 2014), but which were lower compared to the previous report of 83% mortality in KwaZulu-Natal in South Africa. Pietersen et al. (2014) reported thatappropriate long-stay or palliative care facilities for these patients are generally scarce.

1.2.1 Drug resistant -TB treatment in South Africa

Drug-resistant tuberculosis treatment is much more complex for patients to tolerate than treatmentfor drug-sensitive TB. It involves the use of drugs that are costlier, more toxic and less effective (WHO, 2013). The duration of treatment is much longer, usually at least 18-24 months for DR-TB, as opposed to 6 months for drug-sensitive TB. It requires a daily administration of an injectable aminoglycoside (which is very painful) for a minimum of six-months, followed by an 18-24month continuation phase. In South Africa, the national guidelines recommend a 5-drug regimen during a 6-months intensive phase, followed by a 4-drug regimen during the 18 months continuation phase for MDR-TB (DOH, 2011). These regimens and their doses per body weight are shown in Table 1 and Table 2. Treatment for MDR-TB is driven by sputum culture-conversion, whereby treatment is recommended for 18 months after the date of culture-conversion and, in chronic MDR-TB cases, an extension of 24 months is required (WHO, 2008b).

HIV infection further complicates the DR-TB treatment course via the risk of overlapping drug toxicities between antiretrovirals (ARVs) and second-line anti-TB drugs (Satti et al., 2012). A standardised shorter MDR-TB regimen of 9–12 months is now recommendedunder WHO guidelines issued in May 2016 for all patients (excluding pregnant women) with pulmonary multidrug resistant (MDR)/Rifampicin resistant TB (RR-TB) that isnot resistant to second-line drugs. As part of the efforts to improve outcomes for MDR/XDR-TB, at least 70 countries have started using bedaquiline, and 39 countries were using delamanid by the end of 2015

(WHO, 2016).

1.2.2 Drug resistant -TB treatment outcomes in South Africa

Studies have shown that DR-TB is associated with poorer treatment outcomes and frequently associated with a high rate of treatment failure and death (Seung et al., 2009; Brust et al., 2010; Farley et al., 2011; Gandhi et al., 2012; Mukinda et al., 2012; Cox et al., 2014; Schnippel et al., 2015). DR-TB treatment remains challenging and complex, and treatment success is considerably lower than drug-susceptible TB (Orenstein et al., 2009). The cure rate for drug-susceptible TB was (79%) in 2010 in South Africa (WHO, 2012), while the cure rate for DR-TB in South Africa was estimated to be less than 50% (Department of Health, 2009; Schnippel et al., 2015).

In addition to low cure rates, unfavorable treatment outcomes such as default, failure and death have been reported in a few studies conducted in South Africa, especially in HIV-co-infected patients (Holtz et al., 2006; Shean et al. 2008; Brust et al., 2010; Gandhi et al., 2012; Cox et al., 2014). Treatment of DR-TB in HIV-infected patients remains a serious public health challenge (Orenstein et al., 2009; Johnson et al., 2009; Isaakadis et al., 2011). Such patients are required to take large numbers of pills each day, receive intramuscular injections for extended periods of time, and are subject to potentially additive side-effects and drug interactions between antiretroviral agents and second-line anti-tuberculosis drugs (WHO, 2008; WHO, 2009). In addition, mortality is extremely high in HIV-positive drug resistant–TB patients (Cox et al., 2014; Meintjes, 2014).

A knowledge of risk factors for poor DR-TB treatment outcomes is essential for developing effective solutions to improve treatment outcomes. In South Africa limited studies have been done to evaluate DR-TB treatment outcomes and to identify microbiological parameters influencing poor treatment outcomes.

1.3 Motivation for the study

In South Africa, HIV-infected patients with drug-resistant TB are known to have significantly poorer treatment responses and higher mortality rates than HIV-negative patients (Brust et al., 2010; Gandhi et al., 2010; Farley et al., 2011; Cox et al., 2014; Schnippel et al., 2015). Studies have reported that the median sputum culture conversion time was similar in both HIV-positive and HIV-negative MDR-TB patients (Brust et al., 2011; Hafkin et al., 2013). However, treatment default and death suffered by HIV-positive patients affect the sputum culture conversion rate (Issakidis et al., 2011). Sputum culture conversion has been reported as an interim indicator of treatment outcomes, and MDR-TB patients with no sputum culture conversion within two to three months had a high rate of relapse and treatment failure (Seung et al., 2009; Brust et al., 2011). Studies conducted in Europe have reported the median sputum culture conversion time to be 2months (Yew et al., 2000; Holtz et al., 2006; Prasad et al., 2006). Another study conducted in the United States of America reported sputum culture conversion time to be longer in RMR-TB and MDR-TB patients (94 days and 80 days respectively), when compared to Isoniazid mono-resistant TB (HMR-TB) and drug sensitive TB (48 days and 50 days respectively) (Prach et al., 2013). However, a study conducted in the Western Cape in South Africa reported that, between 2001 and 2002, 45% of MDR-TB patients had a median (range) sputum culture conversion time of 5 (2.4- 4.5) months (Shean et al., 2008).

Brust et al (2011) and Hafkin et al (2013), who conducted studies in South Africa and Botswana, have shown that HIV-infected patients could achieve similar sputum culture conversion time as HIV-negative patients at the end of the intensive phase of MDR-TB treatment. In spite of this, the cure rate is poor in MDR-TB patients when compared to drug-sensitive TB. These two investigators only observed short-term microbiological outcomes, and recommended furtherstudies to investigate the impact of HIV-infection on longer-term clinical outcomes in the treatment of MDR-TB. They further recommended additional investigation to discover whether favourable microbiological outcomes predict equally favourable clinical recovery during the end of the continuation phase of MDR-TB treatment. There has been no recent study conducted on the influence of HIV infection on timetosputum culture conversion

during the continuation phase (long-term) treatment of MDR-TB, RMR-TB and HMR-TB patients. It would,therefore, be interesting to see if HIV-infection had any influence on the timetosputum culture conversion during long-term treatment in MDR-TB, RMR-TB, and HMR-TB patients.

Some investigators have revealed that high initial sputum culture colony count, bilateral cavitations on chest radiography, drug regimen, the number of resistant drugs at treatment initiation and low body mass index are independent predictors of longer timetosputum culture conversion in MDR-TB patients (Holtz et al., 2006; Brust et al., 2013; Tierney et al., 2014). A recent study has also revealed that the pattern of drug resistance affects the sputum culture conversion time (Kim et al., 2016). Another recent study revealed that low body mass index was linked to inability to achieve sputum culture conversion in MDR-TB and RMR-TB patients (Velayutham et al., 2016). There are no recent studies that have reported the influence of inappropriate (i.e low and high) anti-tuberculosis drug dose on the timetosputum culture conversion in drug-resistant TB patients. Therefore, it is essential to examine the effect of inappropriate (i.e low and high) anti-TB drug dose on the timetosputum culture conversion in drug-resistant TB patients.

HIV infection has been generally found to significantly lower the treatment success in drug-resistant-TB andcauses a rapid progression of TB to death in both outbreaks and treatment cohorts in South Africa (Brust et al., 2010; Faley et al., 2011; Cox et al., 2014; Schnippel et al., 2015). HIV-co-infected DR-TB patients appear to benefit from antiretroviral treatment, though concurrent management of the treatment of both diseases is complex. Although the combination of tuberculosis treatment and antiretroviral therapy can increase survival in HIV and TB co-infected patients in general, it is less likely to do so in patients with drug-resistant TB in South Africa (Dheda et al., 2004; Gandhi et al., 2012).

Several investigators have confirmed that there is a link between HIV infection and poor treatment outcomes due to a high mortality rate in drug-resistant TB patients (Gandhi et al., 2006; Kliiman and Altraja, 2009; Brust et al., 2010; Farley et al., 2011; Prach et al., 2013; Cox et al., 2014). Poor outcomes and rapid time-to-death have mostly been observed in the absence

of effective antiretroviral treatment (Gandhi et al., 2006; Wells et al., 2007; Seung et al., 2009). A study from KwaZulu-Natal Province, the first extensive study detailing the treatment outcomes of MDR-TB patients in a TB referral hospital in South Africa, reported an association between HIV co-infection and death (Brust et al., 2010). Although the period studiedwas prior to the availability of antiretroviral therapy (ART) in the public sector (2000-2003), they attribute the HIV/deaths to the lack of antiretroviral therapy and recommend an integration of ART with second-line anti-TB treatment in the management of MDR-TB patients. Recent studies have found no association between HIV infection and poor treatment outcomes in MDR-TB (Satti et al., 2012; Marais et al., 2013; Mugabo et al., 2015).

Several authors from Southern Africa have shown in recent studies that the use of antiretrovirals (ARVs) improves the cure rate in MDR-TB patients (Brust et al., 2011; Satti et al., 2012; Hafkin et al., 2013). A recent study conducted in South Africa has reported that the duration of antiretroviral therapy before TB treatment does not influence the treatment outcomes in MDR-TB patients (Mugabo et al., 2015). Another recent study conducted in South Africa revealed a higher mortality rate in HIV-positive patients with MDR-TB who initiated ART before TB treatment (Umanah et al., 2015). More studies are needed on HIV-positive patients before anti-TB treatment to show the effects of antiretroviral treatment on MDR-TB treatment outcomes.

A study conducted in Tugela Ferry in KwaZulu-Natal, South Africa, within a period of 2 years (2005- 2006), reported that a CD4 count of less than 50 cells/mm^3 and a CD4 count between 51-200 cells/mm^3were associated with mortality in MDR-TB patients (Gandhi et al., 2012). A recent study conducted in Lesotho within a period of 5 years (2003-2007) reported poor treatment outcomes in HIV-positive drug-resistantTB patients in which the CD4 count decreased from baseline, or at any point during the treatment (Satti et al., 2013). Limited studies have been done to investigate the effect of changes in CD4 count and viral load at baseline to the end of treatment on DR-TB treatment outcomes in South Africa. Therefore, it is important to look at the influence of changes in CD4 count and viral load,at the baseline to the end of treatment, and at the treatment outcomes in HIV-positive patients with drug-resistant TB in South Africa.

Researchers from South Africa have reported drug-resistant TB to be associated with a significantly higher failure rate and death (Brust et al., 2010; Jacobson et al., 2011; Mukinda et al., 2012; Cox et al., 2014; Schnippel et al., 2015). Brust et al (2010), who conducted a study in KwaZulu- Natal South Africa within a period of 4 years (2000-2003), reported poor treatment outcomes such as failure and death in MDR-TB patients. Mukinda et al (2012), who conducted a study in the Western Cape Province of South Africa on Rifampicin mono-resistant TB over a 5-year period (2004-2008), found an association between RMR-TB and treatment failure. Another study, conducted in the Western Cape Province of South Africa within a 10-year period (2000-2009), found no association between Isoniazid (INH) resistance and outcomes (Jacobson et al., 2011), although it did suggest a poorer outcomefor Isoniazid mono-resistant TB. Schnippel et al (2015), who conducted a study in Gauteng, South Africa within a 3-year period (2009-2011) reported that DR-TB patients receiving second-line drugs were associated with death. There have been limited studies to investigate the influence of drug-resistant TB on treatment outcomes in patients in South Africa. It would thereforebe of interest to see if a significant difference exists between the treatment outcomes in mono-resistance TB cases and MDR-TB cases.

Some researchers have found a link between extrapulmonary TB and poor treatment outcomes in DR-TB patients. A study conducted in South Africa by Gandhi et al (2012) within a two-year period (2005 -2006) involving 186 MDR-TB patients revealed that MDR-TB patients with extrapulmonary TB were more likely to die. Another study conducted in the United States of America by Kurbatova et al (2012) within a four-year period (2000-2003) involving 1786 MDR-TB patients reported extrapulmonary TB to be associated with mortality.Limited studies have been conducted on the influence of DR-TB localization on treatment outcomes in drug-resistant TB patients in South Africa. It would be interesting to investigate the influence of pulmonary TB, extrapulmonary TB, and pulmonary TB and extrapulmonary TB co-infection on the treatment outcomes in drug-resistant TB patients.

The fluoroquinolones are a very important drug class in the treatment of DR-TB and have been shown to improve the cure rate, although development of resistance to quinolones is a concern

(Chigutsa et al., 2012). The national TB programme no longer recommends the use of ofloxacin for the treatment of MDR-TB, instead moxifloxacin is the preferred agent, and in younger children levofloxacin is used (DOH, 2014). However, clinical studies conducted in Southern Africa have found ofloxacin to be less effective than other fluoroquinolones such as moxifloxacin (Zvada et al., 2014; Chigutsa et al., 2012). A pharmacokinetic-pharmacodynamic study of ofloxacin has shown that the currently recommended ofloxacin dose of 800 mg per day is too low for the treatment of MDR-TB in South Africa (Chigutsa et al., 2012), while limited studies have been conducted on the influence of fluoroquinolones on the treatment outcomes in HIV-positive and HIV-negative DR-TB patients.

In Southern Africa ofloxacin has until recently been the fluoroquinolone used in DR-TB, treatment, as the minimum inhibitory concentrations (MICs) of moxifloxacin (0.12-0.50 µg/mL)are lower than those of ofloxacin (1.0-2.0 µg/mL) (Arbex et al., 2010), whilemoxifloxacin exhibits *in vitro* activity, and early bactericidal activity (Arbex et al., 2010). However, there is evidence that moxifloxacin has considerably better activity than ofloxacin (Rustomjee et al., 2008). Since December 2013, South African guidelines have recommended the use of moxifloxacin instead of ofloxacin in an MDR-TB treatment regimen (DOH, 2014). The extent of cross-class resistance is again not entirely clear, with some evidence that moxifloxacin retains activity against some ofloxacin resistance. Zvada et al (2014) and Chigutsa et al (2012) have proposed susceptibility breakpoints of 0.125 mg/liter for 400 mg doses of moxifloxacin and 0.25 mg/liter for 800 mg ofloxacin. They believe that the current dose of 800 mgofloxacin and 400 mg moxifloxacin may be related to poor clinical outcomes. No recent study has investigated the replacement of ofloxacin by moxifloxacin, soit would be interesting to see if the replacement of ofloxacin by moxifloxacin improves treatment outcomes in drug-resistant TB patients.

Consequently, a better understanding of the microbiological parameters influencing DR-TB treatment outcomes should improve the treatment of *Mycobacterial* infections, and provide a more rational use of anti-TB therapy among patients with MDR-TB, RMR-TB, and HMR-TB patients with and without HIV. In this study, the following microbiological and pharmacotherapeutic parameters will be assessed on MDR-TB, RMR-TB, and HMR-TB

treatment outcomes: HIV status, inappropriate (i.e low and high), anti-TB drug dose, sputum culture conversion, sputum culture reversion, immunological and virological profile, ART duration before anti-TB therapy, DR-TB localization, drug resistance and the replacement of ofloxacin with moxifloxacin. It is believed thatconsideration of these parameters in developing therapeutic strategies could improve treatment outcomes in patients with drug- resistant TB, with or without HIV infection.

1.4 Research questions

The key (relevant) questions raised in the literature review are summarized below.

Two studies from Southern Africa have reported similar sputum culture conversion times in HIV-positive and HIV- negative patients with MDR-TB at the end of the intensive phase of MDR-TB treatment (Brust et al., 2011; Hafkin et al., 2013). To the best of my knowledge, no previous study has investigated the time to sputum culture conversion during long-term treatment in HIV-positive and HIV- negative patients in South Africa with MDR-TB, Rifampicin mono-resistant TB, and Isoniazid mono-resistant TB. Hence it would be interesting to describe the sputum culture conversion time in this group of patients.

Secondly, we seek to find out if HIV infection affects the time to sputum culture conversion in drug-resistant TB patients.

Thirdly, we seek to find out whether inappropriate (i.e. low and high) anti-TB drug dose influence the time to sputum culture conversion in drug-resistant TB patients.

Fourthly, we seek to find out whether the changes in CD4 cell count and viral load during treatment which are common in HIV-positive drug-resistant TB patients have any influence on the treatment outcomes.

Fifthly, many of the patients with MDR-TB and co-infected with HIV are on antiretroviral (ARV) therapy, and we would like to find out what influence the duration of antiretroviral therapy before TB treatment has on MDR-TB treatment outcomes.

Sixthly, we seek to compare the treatment outcomes among drug-resistant TB patients.

In addition, since drug-resistant TB patients were treated with either ofloxacin or moxifloxacincontaining regimen, we would like to find out whether the replacement of ofloxacin by moxifloxacin improves the treatment outcomes in these patients.

Lastly, patients with drug resistanceare infected either with pulmonary TB, extrapulmonary TB, or co-infected with pulmonary and extrapulmonary TB, and we would like to find out the influence of pulmonary TB, extrapulmonary TB and co-infection with pulmonary and extrapulmonary on the treatment outcomes in these patients.

The study therefore attempts to answer the following questions:

1. What is the time to sputum culture conversion in drug-resistant TB patients?
2. Could HIV infection affect the time to sputum culture conversion in drug-resistant TB patients?
3. Could inappropriate (i.e. low and high) anti-tuberculosis drug dose influence the time to sputum culture conversion in drug-resistant TB patients?
4. To what extent do changes in CD4 count cells and viral load at base line and 12 months; baseline and 24 months influence the treatment outcomes in HIV-positive patients with drug resistant TB?
5. Could antiretroviral duration before TB treatment influence the treatment outcomes in HIV-positive patients with MDR-TB?
6. Are there differences in treatment outcomes among MDR-TB and mono- resistance cases?
7. Did the replacement of ofloxacin by moxifloxacin improve the treatment outcomes in drug resistant TB patients?
8. Could the fact of having (i) pulmonary TB, (ii) extrapulmonary TB (iii) or co-infection with pulmonary and extrapulmonary have any influence on the treatment outcomes in drug-resistant TB patients?

1.5. Hypothesis

1.5.1 Experimental hypotheses

- There are differences in the time to sputum culture conversion in drug-resistant TB patients
- HIV infection influences the time to sputum culture conversion in drug-resistant TB patients.
- Inappropriate (low and high) anti-tuberculosis drug dose influence the time to sputum culture conversion in drug-resistant TB patients.
- Changes in CD4 count and viral load from baseline to the end of treatment influences the treatment outcomes in drug-resistant TB patients.
- The duration of antiretroviral therapy before TB treatment influences the treatment outcomes in HIV-positive patients with MDR-TB.
- There are differences in the treatment outcomes among drug-resistant TB cases
- The replacement of ofloxacin by moxifloxacin influences the treatment outcomes in drug-resistant TB patients.
- The fact of being infected with either pulmonary TB, extrapulmonary TB or co-infected with pulmonary TB and extrapulmonary TB influences the treatment outcomes in drug-resistant TB patients.

1.5.2 Null hypotheses

- There are no differences in the time to sputum culture conversion in drug-resistant TB patients.
- HIV infection does not influence the time to sputum culture conversion in drug resistant TB patients.
- Inappropriate (low and high) anti-tuberculosis drug dosage does not influence the time to sputum culture conversion in drug-resistant TB patients.
- Changes in CD4 count and viral load from baseline to the end of treatment does not influence the treatment outcomes in HIV- positive patients with drug -resistant TB.
- The duration of the antiretroviral therapy before TB treatment does not affect the treatment outcomes in HIV-positive patients with MDR-TB.
- There are no differences in the treatment outcomes among drug-resistant TB cases.

- The replacement of ofloxacin by moxifloxacin does not influence the treatment outcomes in drug-resistant TB patients.
- The fact of having pulmonary TB, extrapulmonary TB, or co-infection with pulmonary TB and extrapulmonary TB does not influence the treatment outcomes in drug-resistant TB patients.

1.6 Objectives of the study

The objectives of the present study are:

1. To determine the time to sputum culture conversion in drug-resistant TB patients
2. To find out whether HIV infection influences the time to sputum culture conversion in drug-resistant TB patients.
3. To find out if inappropriate (i.e. low and high) anti-TB drug dose influences the time to sputum culture conversion in drug-resistant TB patients.
4. To assess whether changes (increase/ decrease) in CD4 cell count and viral load affects drug-resistant TB treatment outcomes.
5. To find out whether the duration of antiretroviral therapy before TB treatment influences the treatment outcomes in HIV-positive patients with MDR-TB
6. To find out whether there are differences in the treatment outcomes between MDR-TB cases and mono- resistant TB cases.
7. To find out if the replacement of ofloxacin by moxifloxacin improvesdrug-resistant TB treatment outcomes.
8. To find out if the fact of being infected with (i) pulmonary tuberculosis (ii) extra-pulmonary tuberculosis or (iii) co-infection of pulmonary and extrapulmonary tuberculosis influences drug-resistant TB treatment outcomes.

CHAPTER TWO:LITERATURE REVIEW

2.1 Search strategy

Several search strategies were used to identify potentially relevant studies.

1. A systematic search was conducted to identify relevant studies in the following databases: PUBMED (January 2000 to September, 2016), MEDLINE (1999 to 2016), International Pharmaceutical Abstracts (January 1970 to November 2013). Keywords included tuberculosis, Multidrug resistant tuberculosis, Rifampicin mono-resistant TB, Isoniazid mono-resistant TB, DR-TB, XDR-TB, drug-resistant tuberculosis, sputum culture, sputum conversion, sputum reconversion, *Mycobacterium tuberculosis*, low anti-TB drug dose, high anti-TB drug dose, age, antiretroviral agent, extrapulmonary TB, HIV/AIDS, risk factors for MDR-TB and treatment outcomes.
2. Hand-searching of the following journals: *International Journal of Tuberculosis and Lung Disease, American Journal of Respiratory & Critical Care Medicine,* and *Journal of Clinical Infectious Disease*.
3. Bibliographies of full-text articles were examined for relevant studies.
4. Abstracts were included in search results.

2.2 Selection of Studies

Studies obtained from the literature search were checked by title and citation. If an article appeared relevant, the abstract was reviewed. Relevant abstracts were examined in full-text. More than 50 studies were included in the study. Inclusion criteria were as follows: an original study, reported in English; reported treatment outcomes in a population of adult, culture-confirmed MDR-TB, RMR-TB and HMR-TB patients; reported outcomes presented in a format allowing for comparison with other studies. Exclusion criteria were as follows: exclusive surgical series.

2.3 Overview of phenotypic subpopulation of Mycobacterium tuberculosis

*Mycobacterium tuberculosis*is a slow-replicating bacterium with an *invitro*doubling time of about 24 hours in Middlebrook 7H9 liquid media (Straus and Wu, 1980; Ginsberg and Spigelman, 2007), but varying from 18-54 hours under similar growth conditions (Gill et al., 2009). This is in contrast to other bacteria that replicate much more rapidly in culture, for example, such as *Staphylococcus aureus*whichhas a doubling time of about 24 minutes (Domingue et al., 1996). In patients with TB at least 2 different sub-populations have been described in terms of metabolic activity and replication rate: those that are actively replicating and are killed rapidly by anti-tubercular drugs (Jindani et al., 2003), and those that are non-replicating and can lie dormant in the human host for very long periods of time, being less sensitive to the bactericidal activity of drugs (Wayne and Hayes, 1996).Dormant bacteria may result in latent infection for several decades before clinical disease appears (latency) due to decreased immune surveillance or other unknown factors (Lillebaek et al., 2002).

The terms ‘latency’, ‘dormancy’ and ‘persistence’, frequently used interchangeably in this thesis and possibly confusing, are defined by Gomez and McKinney (2004) as follows. ‘Latency’ describes the state of a tuberculous lesion that does not produce clinical symptoms because it is induced by an initially vigorous immune response to contain the infection (Gomez and Mckinney 2004). ‘Dormancy’ relates to the bacteria adopting mechanisms to survive under stressful conditions of low oxygen tension, acidic conditions and amino acid starvation in parts of the lung, and they undergo phenotypic changes whereby they do not replicate. These phenotypic changes also make the bacteria more tolerant of antibiotics (Grant et al., 2012). ‘Persistence’ refers to the ability of *Mycobacteria* to ‘persist’ in the face of harsh conditions, including drug treatment or host immunity (Satria et. al., 2013). The slowly-killed bacteria that remain after the initial killing of actively dividing organisms are frequently called ‘persisters’, which appear to be genetically identical to drug-sensitive organisms but are not replicating (Zhang et al., 2012).

2.3.1 Impact of HIV infection on clinical and microbiological presentation of TB

HIV infection changes the clinical and microbiological presentation of tuberculosis in various ways. Studies have shown that HIV-infected patients have lower *Mycobacterial* colony counts

compared to HIV-negative patients (Mohamed and Naing, 2001; Aderaye et al., 2004). The reduction in colony counts and smear positivity rate in HIV-infected patients make the diagnosis of TB complex among this group of patients and this may have a negative effect on the TB detection process (Aderaye et al., 2004).

A study from the United States of America that analysed 2,953 patients with TB, of which 13.6% were new cases, found that the progression of TB was attributed to HIV infection (Kathryn et al, 2007). Although defects in macrophage function have been demonstrated in HIV-infected patients, there is proof that HIV sero-positive persons are more likely to acquire TB infection than HIV-seronegative individuals, given the same degree of exposure (Hesselings et al., 2009)). In other respects, subclinical infection (positive acid bacilli stains or culture without symptoms and radiological findings) has been found to be most common among ambulatory HIV- infected persons (Mtei et al., 2005).

2.3.2 Impact of tuberculosis on human immunodeficiency virus progression

Tuberculosis is the most common opportunistic infection in HIV-positive patients world-wide (Badri et al., 2001). Studies have shown that TB accelerates progression of the disease in HIV, andthat tuberculosis increases the ability of HIV to replicate by activating CD4-T-lymphocytes and macrophages harbouring latent HIV infection (Day et al., 2004; Kwan et al., 2011). The onset of tuberculosis in HIV-infected patients causes a marked release of proinflammatory cytokines that activate lymphocytes and macrophages, and this results in an increased HIV viral load (Day et al., 2004). Similarly, studies of patients with tuberculosis, and with no access to ART therapy reported that viral load did not decrease, despite effective anti-tuberculosis therapy (Morris et al., 1998; Lawn et al., 1999).

Whalen et al (1995) found a higher mortality rate and a higher incidence of newly-acquired immune deficiency syndrome(AIDS), defining opportunistic infections for HIV-TB co-infected patients, than for HIV-infected patients without active TB who were matched for CD4 cell counts. However, studies assessing the influence of tuberculosis on HIV progression have reported inconsistent results. For example,two of the studies reported that there was a higher mortality and incident rate for new AIDs-defining opportunistic infection for HIV-TB co-

infected patients than for HIV–infected patients without TB who were matched for CD4 cell count (Whalen et al., 1995; Kwan et al., 2011), while other studies have reported either a significantly decreased survival rate (Perneger et al., 1995; Leroy et al., 1997) or an increased incidence of AIDS-defining illness following the diagnosis of tuberculosis in HIV-infected patients (Munsiff et al., 1998).

The synergistic interaction between HIV and TB organisms increases with the level of P24, which implies that TB and its components may activate HIV replication, while stimulation of HIV replication by TB exacerbates dysfunction of host immune responses in dually infected individuals (Zhang et al., 1995).

In addition, TB infection has been shown to elevate expression of HIV co-receptors (CXCR4 and CCR5) that help HIV infection progression, further supporting the idea that blocking these co-receptors may accelerate progression of HIV infection in TB and HIV co-infected patients (Juffermans et al., 2001). Furthermore, opportunistic infections and death are considered to be a greater threat in HIV-infected individuals co-infected with TB than in HIV-infected patients with similar CD4+ cell counts without active TB (Shafer and Edlin 1996).

2.3.3 Effect of human immunodeficiency virus infection on tuberculosis incidence

HIV increases the risk of progression to active TB in both primary and TB infection, and the reactivation of latent TB (Kwan et al., 2011). HIV exacerbates the severity of tuberculosis, greatly increasing the risk of developing the disease in co-infected individuals and leading to more frequent extrapulmonary involvement and atypical radiographic manifestations (Kwan et al., 2011). Although HIV and TB are both treatable and preventable, incidence rates continue to rise in developing nations where HIV infection and TB are endemic and resources are limited.

Furthermore, a study conducted in South Africa amongst gold miners with TB found a linear association between TB incidence and HIV prevalence (Sonnenberg et al., 2005) – a finding which supports the synergistic action between these two infections (Mayer et al., 2010). However, the current predictive models of TB incidence underestimate the effect of HIV in areas

where TB is endemic (Sonnenberg et al., 2005). Another study reported that TB incidence was more strongly associated with HIV infection than the point prevalence of undiagnosed disease, and the researchers attributed that to a rapid increase in TB disease prevalence (Elizabeth et al., 2004).

Although the prevalence and incidence of TB infection is similar for both HIV sero-positive and HIV-sero-negative intravenous drug-users, the risk of active TB is higher in sero-positive subjects (Selwyn et al., 1989). These data suggest that in HIV positive persons, TB most often results from reactivation of latent TB infection, which warrants aggressive chemotherapy against TB in patients with HIV infection and a positive purified derivative (PPD) test.

2.4 Drug-resistant TB

2.4.1 Mechanism of drug resistance

There are two mechanisms by which a patient may acquire MDR-TB.Firstly,there is primary resistance whereby a patient who has not previously been treated for TB becomes infected with a drug-resistant strain of *Mycobacterium tuberculosis (*Friedland, 2007a). The second mechanism is acquired resistance, where a patient has been treated for TB on one or more occasions, so that resistance is likely to have been caused by an insufficient amount of one or more anti-mycobacterial drugs (Friedland, 2007a). The insufficient amount or improper use of anti-TB drugs may be caused by poor patient compliance, poor quality medicines, or the administration of inappropriate treatment regimens, for example in areas with poor TB control programs (WHO, 2013b). Inadequate drug levels select for resistant mutants, and once patients have resistance to one of the drugs, they are more likely to develop resistance to other drugs (Friedland, 2007a).

2.4.2 Factors influencing bacterial drug resistance

Several authors from Europe and the United States of America have reported previous TB history and treatment as one of the factors influencing bacteria drug resistance (Sandman et al., 1999; Leimane et al., 2005; LoBue and Moker, 2005; Faustini et al., 2006; Cattamanchi et al., 2009; Kliiman and Altraja, 2009). Studies conducted in sub-Saharan Africa have also reported

previous TB treatment as a factor influencing bacterial drug resistance in high HIV-prevalence settings (Schreiber et al., 2009; Cox et al., 2010; Sanchez- Padilla et al., 2012; Asres et al., 2013). According to Sanchez-Padilla et al (2012), TB treatment history has been strongly associated with MDR-TB, and this also suggests that MDR-TB may have been acquired during a previous treatment episode. Such an acquired drug resistance may signify a failure of TB control programmes due to inadequate case management, interruption in drug supply or inadequate drug regimens. A meta-analysis of 22 clinical studies in Africa also reported previous TB treatment to be associated with MDR-TB (Viswanathan, 2008). Cattamanchi et al (2009) and Fox et al (2011) report a link between previous TB history and Isoniazid mono-resistant TB. According to a study by Espinal et al (2000), the likelihood of MDR-TB increased gradually, along with the length of the previous treatment period. The longer the TB treatment, the more likely its becoming unstandardized or interrupted and, consequently, the higher the probability of generating strains resistant to the selected drugs.

Another factor influencing bacterial drug resistance is age-group. Some authors from Europe have demonstrated a clear association between MDR-TB and the under-65 year (22-45 years) age group (Faustini et al., 2006; Suarez- Gracia et al., 2006). Similar reports have emanated from South Korea, where MDR-TB has been significantly related to those under 45 years old (Choi et al., 2007). A recent South African study conducted by Mugabo et al. (2015) revealed that MDR-TB was associated with the 25-50 years age group (Mugabo et al., 2015). Some investigators in South Africa have reported Rifampicin mono-resistant TB to be linked to the occurrence of infections in those older than 40 years of age (Mukinda et al., 2012). In contrast is another study conducted in South Africa, which reported RMR-TB to be more likely in the age range of 25-29 years (Coovadia et al., 2013). The magnitude of drug resistance among younger age-groups is more likely to be indicative of recent transmission than among older age-groups, which are more likely to be harboring older infections (WHO, 2009).

The issue of gender in association with developing DR-TB is also interesting. According to a report by Faustini et al (2006), it has been demonstrated in Western Europe that MDR-TB patients were more likely to be males. Furthermore, it has been hypothesized that women are more compliant with treatment and therefore less likely to receive inadequate treatment. By contrast, in some reports from the former Soviet Union, where the risk of transmission of drug-

resistant TB is greater because of the wide spread of MDR-TB infection, female sex was found to be a predictor of MDR-TB (Mdivani et al., 2008; Suchindran et al., 2009). According to a meta-analysis of 22 clinical studies conducted in Africa, MDR-TB was reported to be associated with the female gender in Equatorial Guinea (Viswanathan, 2008). Another study conducted in South Africa reported that MDR-TB was more common amongst males (Mugabo et al., 2015). Studies conducted in South Africa have revealed that Rifampicin mono-resistant TB patients were more likely to be male (Mukinda et al., 2012; Coovadia et al., 2013).

There has been conflicting evidence about whether HIV infection is a risk factor for MDR-TB. A recent study conducted in Swaziland demonstrated a positive association between HIV and MDR-TB (Sanchez-Padilla et al., 2012), while other researchers found no association between HIV-infection and MDR-TB (Viswanathan, 2008; Suchindran et al., 2009; Asres et al., 2013; Mugabo et al., 2015). A more recent report has revealed that HIV is not a risk factor for MDR-TB and that the prevalence of TB has been increasing among patients who were HIV-negative (Chuchottaworn et al., 2015). Studies have also reported an association between RMR-TB and HIV infection (Munsiff et al., 1997; Sandman et al., 1999;Dramowski et al., 2012; Mukinda et al., 2012; Coovadia e al., 2013). Studies have also reported an association between RMR-TB and lower CD4 cell counts, extrapulmonary TB disease, noncompliance, and use of anti- fungal drugs (Munsiff et al., 1997; Ridzon et al., 1998; Vernon et al., 1999; Mukinda et al., 2012).A study conducted in the United States of America reported no link between HIV infection and Isoniazid mono-resistant TB (Cattamanchi et al., 2009).

The most likely reasons linking drug-resistant TB to HIV are numerous. The first is the acquisition of rifampicin-resistance among HIV-infected patients under treatment for TB. Malabsorption of certain anti-TB drugs, particularly, of rifampicin and ethambutol, has been reported in settings where HIV-prevalence is high (WHO, 2008). This suggests that HIV-positive TB patients may be at greater risk of acquiring resistance due to their decreased bioavailability of the respective drugs which, in terms of the performance of the drugs,is equal to the effect of intermittent therapy (Kliiman and Altraja, 2009). The second reason is related to ‘common exposures’ whereby HIV-positive patients and drug-resistant TB patients may share risk factors such as a history of hospitalization, intravenous drug abuse, previous imprisonment, socioeconomic distress, and alcohol abuse (Kliiman and Altraja, 2009).

Another factor is the specific genotype of *Mycobacterium tuberculosis* strain. The Beijing genotype family has been shown to have an association with drug resistance (Bifani et al., 2002; Marais et al., 2006). The worldwide distribution of this family strain has led to assumptions that it has a selective advantage over other clinical isolates in causing disease (Bifani et al., 2002). In addition, a genotype family of *Mycobacterium tuberculosis* strains characteristic of South Africa has been linked to anti-TB drug resistance in KwaZulu-Natal Province, where XDR-TB emerged as a major public health concern (Gandhi et al., 2006).

2.4.3 Factors influencing sputum culture conversion rate in drug-resistant TB patients

2.4.3.1 Factors influencing sputum culture conversion rate in MDR-TB patients

Sputum cultures are an important tool in monitoring the response to tuberculosis (TB) treatment, especially in multidrug-resistant tuberculosis (Tierney et al., 2014). According to Tierney et al (2014), sputum culture conversion is the transition in sputum culture which results from a positive sample growing *Mycobacterium tuberculosis* to two consecutive negative cultures separated by at least 30 days, which is a key clinical milestone signifying that the patient is responding to therapy. It is known that culture conversion can be delayed in the treatment of MDR-TB, as compared to drug-susceptible disease (Tierney et al., 2014).

Recent studies have shown that HIV infection is not a risk factor in delaying sputum culture conversion among MDR-TB patients during the intensive phase of treatment (Seung et al., 2009; Brust et al., 2011; Hafkin et al., 2013). However, other studies have shown that HIV infection is associated with rapid time to sputum culture conversion in MDR-TB patients (Brust et al., 2011; Basit et al., 2014; Tierney et al., 2014). Recent studies have reported similar time and rate of sputum culture conversion between HIV-positive and HIV-negative MDR-TB patients at the end of the intensive phase of treatment (Brust et al., 2011; Hafkin et al., 2013).

Another important factor is the presence of advanced pulmonary disease, such as respiratory difficulty and tachycardia. These advanced pulmonary diseases have been associated with lower rates of conversion, possibly due to higher bacterial burdens in MDR-TB patients (Tierney et al.,

2014). A study of 56 MDR-TB patients conducted in South Africa by Brust et al (2013) found that patients with cavitary disease and consolidation on base-line chest radiography were associated with a longer time to sputum culture conversion. They also reported positive baseline sputum smear to be associated with longer time to sputum culture conversion in MDR-TB patients. Otherinvestigators reported lung cavitation at baseline and chest x-ray as predictors of longer time to sputum culture conversion (Basit et al., 2014).

According to a recent study, culture conversion occurs more slowly in patients with low body-weight (Tierney et al., 2014). A recent study has revealed that a low body mass index (BMI) is associated with the inability to achieve sputum culture conversion in MDR-TB patients (Velayutham et al., 2016). It revealed that patients with body mass index (BMI) <16 kg/m2 and patients with body mass index (BMI) <16-18 kg/m2 were less likely to have culture conversion. Another investigator reported female sex, no previous history of TB and increased weight to be associated with shorter time to sputum culture conversion in HIV-negative patients with MDR-TB (Loveday et al., 2012). Other investigators reported previous TB treatment and incarceration as predictors of longer time to sputum culture conversion in MDR-TB patients (Holtz et al., 2006).

Different studies have reported the use of prothionamide, resistance to second-line anti-TB drugs and first-line anti-TB drugs such as fluoroquinolones, kanamycin, pyrazinamide, ofloxacin, and streptomycin as predictors of delayed culture conversion in MDR-TB patients (Leimane et al., 2005; Holtz et al., 2006; Guler et al., 2007; Basit et al., 2014; Tierney et al., 2014).

2.4.3.2 Factors influencing sputum culture conversion rate in Rifampicin mono-resistant TB patients

It is known that culture conversion can take longer in the treatment of Rifampicin mono-resistant TB (RMR-TB) patients when compared to drug susceptible disease. A study conducted in the United States of America reported culture conversion to be longer in patients with RMR-TB as compared to drug sensitive TB (Prach et al., 2013). The median time to sputum culture conversion reported by the authors was 93.5 days (IQR 42.0-162.0) in RMR-TB patients and 50 days (27.0–81.0) in drug-sensitive TB cases. The investigators documented culture conversion in 77.1% of the 160 RMR-TB patients involved in the study. Another study from the United States

of America documented culture conversion in 50% of the 11 RMR-TB patients involved in the study (LoBue and Moser, 2005).

A recent study has revealed that low body mass index (BMI) affects the time to sputum culture conversion in Rifampicin-resistant TB patients (Velayutham et al., 2016). They show that patients with body mass index (BMI) <16 kg/m2 and patients with body mass index (BMI) <16-18 kg/m2 were less likely to have culture conversion. There have been limited studieson the time to sputum culture conversion in Rifampicin mono-resistant TB patients.

2.4.3.3 Factors influencing sputum culture conversion rate in Isoniazid mono-resistant TB patients

A study conducted in the United States of America has shown that culture conversion time can be almost similar between patients with Isoniazid mono-resistant TB (HMR-TB) and patients with drug sensitive-TB (Prach et al., 2013). The investigators reported a median time of 48 days (IQR 26-84) in HMR-TB patients and 50 days (27.0–81.0) in drug-sensitive TB patients. The authors documented culture conversion in 82.9% of the 3434 HMR-TB patients involved in the study. Another study conducted in the United States of America documented culture conversion in 71% of the 287 patients in their study (LoBue and Moker, 2005). Another study in Taiwan documented a culture conversion rate of 73.7% of the 395 HMR-TB patients involved in the study (Chien et al., 2015).There have been very limited studies conducted on the time to sputum culture conversion in Isoniazid mono-resistant TB patients.

2.4.4 Factors influencing sputum culture reversion rates in drug-resistant TB patients

Very few studies have been reported on sputum reversion in DR-TB patients. Culture reversion has been described in cases of MDR-TB (Holtz et al., 2006; Kurbatova et al. 2011,; Janssen et al., 2012). Holtz et al (2006) reported 14 cases (an 11% reconversion rate) in their study, with 13 patients having successful outcomes and only 1 patient failing the treatment. They also reported previous treatment of MDR-TB as a risk factor for sputum reversion in MDR-TB patients. Another group of researchers reported that the mean time to sputum reversion was 11.3± 6.3 months after the start of MDR-TB treatment, reporting a culture reversion rate of 23.7% in their study (Kurbatova et al., 2011).Other investigators highlighted the effects of sputum reversion at different intervals during the treatment of MDR-TB patients (Janssen et al., 2012), reporting that

the sputum cultures of 11.6% of patients reverted to positive within 1 month following the initial negative culture result. These investigators reported that an additional 5.4% reverted after two consecutive negative cultures. Importantly, in 60.9% of patients with a reversion, the sputum culture returned negative within 1 month. In all of these patients, the sputum culture returned negative within 4 months of treatment.

2.4.5 Causes of Relapse

Relapse is defined as the case when patients who were previously treated for TB were declared cured or their treatment completed after their most recent treatment, and are now diagnosed with recurrent episodes of TB (WHO, 2013). Relapse can be caused by the same strain of *Mycobacterium tubeculosis* that caused the previous TB episode. However, caution is required when differentiating between the recurrence of a TB infection due to relapse and a reinfection. DNA fingerprinting can help to identify the strain of the *Mycobacterium* and thereby distinguish between the two scenarios (Sonnenberg et al., 2001).

Since the treatment of TB is relatively long (at least 6 months) and the time needed to investigate relapse is a further 1-2 years, surrogate endpoints have been investigated in an attempt to conduct feasible and realistic studies for following up patients, butthis is associated with increased study costs and feasibility problems, such as patient dropout and increased amounts of missing data. A negative sputum culture result after 8 weeks of treatment is widely accepted as a surrogate endpoint for sterilizing activity (Mitchison, 1993).

2.5 Drugs used for treating drug resistant TB in South Africa

According to South African guidelines, the standardized treatment regimen for MDR-TB consists of a six-month daily intensive phase with five anti-TB drugs. An aminoglycoside (Kanamycin), a thionamide (ethionamide), pyrazinamide, a fluroquinolone (ofloxacin/moxifloxacin), ethambutoland terizidone, followed by a 12- 18 month continuation phase with three drugs (ethionamide, ofloxacin/moxifloxacin,), and either ethambutol or terizidone (Weyer, 2005). It has been recommended that these anti-TB drugs be administered five times per week in out-patient clinics and seven times per week in hospitals (DOH, 2013).

The first line anti-TB drugs added to the standardized MDR-TB treatment are Pyrazinamide and

Ethambutol (DOH, 2013). The treatment for Rifampicin-mono-resistant TB is a standardized regimen of MDR-TB plus Isoniazid, with a minimum duration of 18 months after culture conversion (DOH, 2013).

The treatment of Isoniazid mono-resistant TB is usually within 6 - 9 months, based on symptomatic response to treatment, weight gain and sputum culture combinations (DOH, 2013). A minimum of 6 months after culture conversion is adequate (DOH, 2013). Regimen I or II is used in the intensive phase for the full duration of treatment (except for Isoniazid) (DOH, 2013).

Second- line drugs used in intensive and continuation phases, and the dosages of these drugs,are shown in Tables 1 and 2.

Table 1:Standardised National MDR-TB Treatment Regimen for Adults and Adolescents (Intensive phase) (DOH, 2013)

Patients weight	Drug	Daily dosage mg/kg
33 kg	Kanamycin	15-20 mg/kg
	Moxifloxacin	400 mg
	Ethionamide	15-20 mg/kg
	Ethambutol	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
33-50 kg	Kanamycin	15-20 mg
	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Ethambutol	800 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51-70 kg	Kanamycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Ethambutol	1000 mg
	Terizidone	750 mg
	Pyrazinamide	1750-2000 mg
>70 kg	Kanamycin	1000 mg
	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Ethambutol	1200 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

Table 2: Standardised National MDR-TB Treatment Regimen for Adults and Adolescents (Continuation phase) (DOH, 2013)

Patients weight	Drug	Daily dosage mg/kg
33 kg	Moxifloxacin	400mg
	Ethionamide	15-20 mg/kg
	Terizidone	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
33-50 kg	Moxifloxacin	400 mg
	Ethionamide	500 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
51-70 kg	Moxifloxacin	400 mg
	Ethionamide	750 mg
	Terizidone	750 mg
	Pyrazinamide	1000-1750 mg
>70 kg	Moxifloxacin	400 mg
	Ethionamide	750-1000 mg
	Terizidone	750-1000 mg
	Pyrazinamide	2000-2500 mg

2.5.1 Pharmacology of anti-tuberculosis drugs used for treating drug- resistant TB patients

2.5.1.1 Rifampicin

Rifampicin is one of the most active anti-tuberculosis agents known, and is also effective against most gram-positive bacteria, as well as many gram-negative species (Rang et al., 2012). It enters phagocytic cells and can therefore kill intracellular microorganisms, including the tubercle bacillus. Rifampicin acts by binding to, and inhibiting, DNA- dependent RNA polymerase in prokaryotic but not in eukaryotic cells (Rang et al., 2012). The oral bioavailability is reduced by food and by first-pass metabolism. It is well distributed, with cerebrospinal fluid (CSF) concentrations reaching 10-20% of the plasma concentrations (Rossiter, 2010). Protein binding

is 80-90% and rifampicin has a half-life of 2.5 hours (which is increased in hepatic disease). It is metabolized rapidly in the liver and undergoes autoinduction. Rifampicin and its active deacetylated metabolite are eliminated chiefly via the biliary-faecal route, 60-65% is excreted unchanged in the faeces and the remainder in the urine (Rossiter, 2010).

Adverse effects of rifampicin include induction of hepatic metabolizing enzymes, which increases the degradation of warfarin, glucocorticoids, narcotic analgesics, oral anti-diabetic drugs, dapsone and oestrogens (Rang et al., 2012). Gastro-intestinal disturbances, and liver damage with jaundice,has been reported and has proved fatal in a very small proportion of patients, and liver function should be assessed before treatment is started (Rang et al., 2012)

Rifampicin may cause an orange discolouration of body fluids such as saliva, sputum, sweat and tears (Rang et al., 2012). Rifampicin should be used with caution in patients with pre-existing hepatic dysfunction and porphyria, and in patients taking other hepatotoxic drugs or alcohol (Chambers, 2004). The level of these drugs may be decreased and may drop below therapeutic levels, requiring dosage adjustment. The drugs involved include: protease inhibitor (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), phenytoin, warfarin, oral contraceptives and digoxin (Rossiter, 2010).

The usual adult dose is 10 mg/kg orally (PO) or by intravenous injection (IVI) as a single daily dose (Chambers, 2004). In patients with liver impairment, the total daily dose should not exceed 8 mg/kg and in paediatrics the usual dose is 15 (range 10-20) mg/kg/day (WHO, 2014).

2.5.1.2 Isoniazid

Isoniazid is bacteriostatic and it is a pro drug that is activated by the *Mycobacterial* enzyme katG (Rang et al., 2012). It is active against growing tubercle bacilli and it enters the *Mycobacterial* cells by passive diffusion (Rang et al., 2012). As well as being used in the treatment of TB, it is used prophylactically in Isoniazid Preventative Therapy (IPT). Oral absorption of isoniazid is good, although this is decreased when taken simultaneously with food or antacids (Rossiter, 2010). It is widely distributed, via tissues and body fluids, including the CSF and is excreted in the urine partly as unchanged drug and partly in the acetylated or otherwise inactivated form

(Rang et al., 2012).

Isoniazid penetrates well into 'caseous' tuberculous lesions (i.e. necrotic lesions with a cheese-like consistency). Metabolism involves acetylation, and depends on genetic factors that determine whether a person is a slow or rapid acetylator of the drug, with slow inactivators enjoying a better therapeutic response (Rang et al. 2012). The half-life in slow inactivators is 3 h and 1 h in rapid inactivators (Rang et al., 2012).

Isoniazid is hepatotoxic and may cause haematological changes, arthritic symptoms, fever and vasculitis. It affects the central and peripheral nervous systems, largely due to pyridoxine deficiency, which is common in malnourished patients (Rang et al., 2012). Isoniazid may cause haemolytic anaemia in individuals with glucose 6-phosphate dehydrogenase deficiency (Rang et al., 2012).

Due to the hepatotoxic nature of isoniazid, caution is exercised in patients with pre-existing liver impairment or porphyria, and in patients taking other potentially hepatotoxic drugs or alcohol (Rang et al., 2012).

Drug interactions are common with isoniazid use, due to the fact that isoniazid is an inhibitor of certain cytochrome P450 enzymes. Isoniazid will inhibit the metabolism of phenytoin, carbamazepine, warfarin, and theophylline, and hence their doses may need to be reduced in order to prevent toxicity (Rossiter, 2010). Studies conducted in South Africa have reported that the high dose of INH, used in the treatment of MDR-TB that is caused by TB isolates do not have *KatG* mutations but *inhA* promoter mutation (Muller et al., 2011; Niehaus et al., 2015). These two investigators reported that the prevalence of *inhA* mutation without a *KatG* mutation in MDR-TB isolates was 40% and 14.8% respectively (Muller et al., 2011; Niehaus et al., 2015). The concurrent use of isoniazid with rifampicin, paracetamol or alcohol may potentiate hepatotoxic effects. In adults, isoniazid is dosed at 5 mg/kg daily as a single oral dose and in paediatrics 10 (range 7-15) mg/kg/day (WHO, 2014). In TB meningitis (TBM) and miliary TB, 20 mg/kg/day may be given. When INH is given as prophylaxis (IPT), the dose is 10 mg/kg daily (maximum 300 mg/day) (Rossiter, 2010).

2.5.1.3 Ethambutol

Ethambutol is bacteriostatic, but may be bactericidal at higher doses. It is hypothesized that it exerts its effect by inhibiting ribonucleic acid (RNA) synthesis in actively dividing *Mycobacteria* (Rossiter, 2010). It is used in the treatment of drug sensitive TB and drug resistance TB, and has low toxicity and good tolerance (DOH, 2011). Ethambutol is evenly distributed except in the CSF. It has an elimination half-life of 3-4 hours in healthy patients, which is increased in patients with renal impairment. Approximately 15% is metabolized in the liver, and it is eliminated chiefly by the excretion of the unchanged drug in the urine (DOH, 2011).

The most common adverse effects of ethambutol are optic neuritis and hyperuricaemia (which may cause arthralgia and gout). Other less common adverse effects are gastrointestinal disturbances, peripheral neuropathy and skin rashes. The use of ethambutol is contra-indicated in patients with advanced renal failure and in those with optic neuritis (Rossiter, 2010). Caution is applied when used in patients with renal impairment and eye defects. Ethambutol is not recommended for use in children younger than 8 years old, except in severe cases where the benefit outweighs the risk. Ethambutol interacts with PZA and thiazide diuretics, causing an increased risk of elevated serum urate levels. When used with other neurotoxic drugs, the risk of optic and peripheral neuritis is increased (Rossiter, 2010).

In adults, ethambutol is given at a dose of 15 mg/kg orally once daily, in paediatrics ethambutol is given at a dose of 20 (15-25) mg/kg with doses of up to 25 mg/kg being used for TB meningitis (WHO 2014). In geriatric patients, the lowest dosing range should be used (maximum 15 mg /kg daily) and in patients with renal impairment the dosage intervals should be increased (Rossiter, 2010).

2.5.1.4 Aminoglycosides (Streptomycin/Amikacin/Kanamycin)

Streptomycin was the first anti-mycobacterial drug to be discovered. Aminoglycosides exert their antimicrobial action by inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit and are bactericidal against actively dividing bacteria (DOH, 2011). Following intramuscular (IM) injection, peak concentrations of aminoglycosides in the plasma

are reached in approximately 30-90 minutes. This class of drugs exhibits concentration-dependent killing and a significant post-antibiotic effect; thereforeit is recommended that they be given as a single daily dose (Chambers, 2004). Aminoglycosides are cleared via the kidneys and have a half-life of approximately 2-3 hours in patients with normal renal function. Therapeutic drug monitoring is useful in patients with renal impairment so as to avoid or minimise accumulation and toxicity, but dosing intervals may need to be increased, depending on plasma levels (Rossiter, 2010).

The most severe adverse reaction caused by aminoglycosides is ototoxicity due to damage to cranial nerve VIII, including vestibular damage (vertigo, ataxia, and nystagmus) and cochlear damage that can lead to hearing loss (Arbex et al., 2010). The other side effect is nephrotoxicity, which is seen in patients with renal impairment or those taking other nephrotoxic agents concurrently. The concurrent use of aminoglycosides with other nephrotoxic or ototoxic drugs is not recommended, due to the additional potential for toxic effects (Arbex et al., 2010). Hypersensitivity reactions and CNS effects such as headaches may also occur. Aminoglycosides are contra-indicated in patients who are hypersensitive to them and they are not recommended for use in pregnancy as they cross the placenta and may cause fetal ototoxicity. They should be used with caution in patients with renal impairment, hearing impairment and myasthenia gravis (Rossiter, 2010).

The usual adult dose for aminoglycosides is 15 mg/kg. In patients with renal impairment, the dosing interval should be prolonged and the dose reduced according to existing plasma levels. Streptomycin is given by intramuscular (IM) injection only, amikacin and kanamycin may be given IM or intravenously (IV) (Rossiter, 2010).

2.5.1.5 Ethionamide

Ethionamide is bacteriostatic at the usual dose, but bactericidal at higher concentrations (Arbex et al., 2010; DOH, 2011). Ethionamide acts on intracellular and extracellular bacilli. The MIC of ethionamide for *Mycobacterium tuberculosis* is in the range of 0.6-2.5 μg/mL (Arbex et al., 2010). Ethionamide is widely distributed throughout the whole body, including the CNS (Coyne et al., 2009). It has a half-life of two hours and is metabolized mainly in the liver. Ethionamide

is metabolized in the liver and excreted in the urine, 1-5% being excreted as an active drug (unaltered) and the remainder being excreted as metabolites (Arbex et al., 2010).

The most common adverse effects are gastrointestinal, including a metallic taste in the mouth, excessive salivation, nausea, vomiting (severe), loss of appetite and abdominal pain (Arbex et al., 2010). These symptoms may improve if the drug is taken at mealtime or at bedtime. CNS effects such as psychosis, depression and anxiety may also occur. The use of ethionamide is contra-indicated in patients hypersensitive to the drug, as well as patients with severe hepatic dysfunction and porphyria. Caution should be exercised when using ethionamide in patients with a history of psychiatric illness, epilepsy, diabetes or hypothyroidism (Rossiter, 2010).

The concurrent use of ethionamide with isoniazid will result in increased risk of neurological side-effects. When it is used with cycloserine or terizidone, there is an increased risk of CNS side-effects. In adults and children older than 10 years, the usual dose is 15-20 mg/kg daily as a single oral dose (maximum 1 g/day). Patients with renal impairment with a glomerular filtration rate (GFR) of less than 10 ml/min should be given 50% of the normal dose. Children younger than 10 years are given 15-20 mg/kg daily (this may be increased to 20 mg/kg daily in military TB or TB meningitis) (WHO, 2014).

2.5.1.6 Fluoroquinolones (Moxifloxacin/Ofloxacin/Levofloxacin)

Fluoroquinolones are bactericidal and show different degrees of effectiveness against *Mycobacterium tuberculosis* (Arbex et al., 2010). Moxifloxacin is preferred in the treatment of MDR and XDR-TB, but ofloxacin and levofloxacin are preferred in patients younger than 8 years old (DOH, 2011). Fluoroquinolones are well absorbed following oral administration and distributed widely in the tissues. They are excreted renally. The half-life of ofloxacin and levofloxacin is 5-7 hours, while the half-life of moxifloxacin is 9-10 hours (Chambers, 2004). In *in vitro* the minimum inhibitory concentrations (MICs) for ofloxacin and moxifloxacin are in the range of 1.0-2.0 ug/ml and 0.12- 0.25 ug/ml respectively (Arbex et al., 2010).

The fluoroquinolones are generally well tolerated, with common adverse effects being gastrointestinal, such as nausea, abdominal discomfort, anorexia, vomiting and diarrhoea (Arbex

et al., 2010). Central nervous effects such as dizziness, headache, insomnia and tremor may occur (Arbex et al., 2010). Quinolones are contraindicated in patients who have a known allergy or sensitivity to them. Caution should be exercised when using them in patients with hepatic or renal impairment or in patients under 18 years old, as they may damage growing cartilage. They are not recommended for use in pregnant or lactating women (Rossiter, 2010). Fluoroquinolones should not be taken with antacids or minerals such as calcium, iron or magnesium, as they may interfere with the drug and reduce absorption (Chambers, 2004). Levofloxacin is given to adults in a dose of 7.5-10 mg/kg daily (maximum 1000 mg/day) and to children younger than 5 years old in a dose of 10 mg/kg twice daily. Children older than 5 years are given 10 mg/kg once daily. The adult dose for moxifloxacin is 400 mg daily (orally or IV), and the dose for children is 7.5 mg-10 mg/kg daily. Ofloxacin is dosed at 800 mg daily for adults (oral or IV) (DOH, 2011).

2.5.1.7 Terizidone/Cycloserine

Terizidone is a cycloserine derivative but has a lower incidence of side-effects than cycloserine. Terizidone is a combination of 2 molecules of cycloserine (DOH, 2011). It is bacteriostatic at the normal dose and inhibits *Mycobacterial*cell wall synthesis by interfering with peptidoglycan pentapeptide production (Arbex et al., 2010). Terizidone shows good absorption and distribution into tissues and fluids including the CSF (Rossiter, 2010). Only a small proportion of terizidone/ cycloserine is metabolized in the liver and the majority of the dose is excreted in the kidneys via active form into the urine. Terizidone is bacteriostatic and the minimum inhibitory concentrations (MICs) of cycloserine/terizidone for *Mycobacterium tuberculosis* are in the range of 5-20 mg/mL (Arbex et al., 2010).

Terizidone commonly causes a series of neurological side-effects such as headache, mental confusion, convulsion, dysarthria and vertigo (Arbex et al., 2010). These occur especially when the daily dose is higher than 500 mg or when cycloserine/terizidone is concomitantly administered with other neurotoxic drugs, such as isoniazid and ethionamide (Arbex et al., 2010). High dose pyridoxine (150 mg) should be given concomitantly to minimize neurological side-effects (DOH, 2011). Terizidone use is contra-indicated in patients with porphyria, psychosis, depression, epilepsy and severe renal impairment (Arbex et al., 2010). It is given to adults at a dose of 10-20 mg/kg daily orally (maximum 1000 mg/day) (DOH, 2013. The dosing interval should be prolonged for patients with renal impairment (Rossiter, 2010).

2.5.1.8 Pyrazinamide

One key characteristic of pyrazinamide (PZA) is its ability to inhibit semidormant bacilli residing in acidic environments (Jnawali et al., 2013). Many MDR-TB patients have chronically inflamed lungs, which also theoretically provide an acidic environment. It inhibits *Mycobacteria* at concentrations of approximately 20 mcg/ml (Chambers, 2004). It has a sterilizing effect and is active against dormant bacteria, thereby allowing the treatment period to be shortened and playing a crucial role in the treatment of *Mycobacterium tuberculosis.*

PZA activity is quite poor, with minimum inhibitory concentrations (MICs) in the range of 6.25-50 μg/ml (Jnawali et al., 2013). PZA is a structural analogue of nicotinamide and is a pro-drug that needs to be converted into its active form, pyrazinoic acid, by the enzyme pyrazinamidase/nicotinamidase (PZase) (Jnawali et al., 2013). Recent research shows that PZA is only active against *Mycobacterium tuberculosis* at acid pH 5.5 (Jnawali et al., 2013).

PZA is only used in the treatment of *Mycobacterial*infections and is used in combination with other anti-TB drugs. The drug is well absorbed from the gastrointestinal tract and widely distributed, reaching concentrations in the CSF equal to those in the plasma. It has a half-life of 9-10 hours, and 4-14% of the drug is eliminated unchanged in the urine, the remainder as metabolites formed in the liver (Rossiter, 2010).

The most significant side-effect noted is dose-related hepatotoxicity, as well as gastrointestinal tract side-effects such as nausea, vomiting and diarrhoea, although these may be minimized if the drug is taken with meals. It may also cause hyperuricaemia (due to PZA inhibiting uric acid clearance) and this may be associated with arthralgia (Rossiter, 2010). Liver function tests and serum uric acid levels should be regularly monitored. Photosensitivity, thrombocytopenia, and sideroblastic anaemia are rare. PZA is contraindicated in patients with porphyria, or those with severe hepatic damage, and should be used with caution in patients with gout, diabetes, renal impairment, and in patients who exhibit hypersensitivity to PZA, isoniazid, ethionamide or niacin. PZA inhibits urate clearance, and therefore allopurinol and probenicid dosages may need to be adjusted if used concurrently. When PZA is used with diuretics and ethambutol, there is an increased additive potential for serum urate levels to be elevated (Rossiter, 2010).

The adult dose of PZA is 20-30 mg/kg/day (maximum of 2 g/day) (DOH, 2011). With patients with renal impairment, the dose at the lower limit of the recommended range should be used, although if the patient's GFR is less than 10 ml/min the dose may be reduced by up to 50%. In paediatric patients the dose used is 35 (30-40) mg/kg daily (up to 40 mg/kg/day in TB meningitis, miliary and MDR-TB) (WHO, 2014).

2.5.1.9 Para-aminosalicylic acid

Para-aminosalicylic acid (PAS) was one of the first antibiotics to show anti-TB activity and was used to treat TB in combination with isoniazid and streptomycin (Jnawali et al., 2013). Later, with the discovery of other more potent drugs including rifampicin, its use in first line regimens was discontinued (Jnawali et al., 2013). Para-aminosalicylic acid is bacteriostatic, it acts preferentially on extracellular bacilli (Arbex et al., 2010). The drug can currently be administered in granules stored in 4-mg envelopes, replacing the former 500-mg capsules. The MIC of the drug for *Mycobacterium tuberculosis* is in the range of 1-5 μg/mL (Chhabra et al., 2011). The mechanism of action of para-aminosalicylic acid has yet to be elucidated and it is believed that the mechanism is related to interference with bacterial folic acid synthesis and inhibition of iron intake (Arbex et al., 2010). It is well absorbed following oral administration. The half- life of para-aminosalicylic acid is 1 hour, it is metabolized in the intestines and liver, via acetylation, into N- acetyl- para- aminosalicylic acid. PAS is excreted renally (Arbex et al., 2010).

Common adverse effects of PAS are gastrointestinal, such as anorexia, diarrhoea, nausea, and vomiting (Arbex et al., 2010). Hypothyroidism may occur, especially when para-aminosalicylic acid is administered concomitantly with ethionamide (Arbex et al., 2010). Para- aminosalicylic acid should be used with caution in patients with glucose-6- phosphate dehydrogenase deficiency and in those who are allergic to aspirin (Arbex et al., 2010). Para-aminosalicylic is contraindicated also in patients with severe kidney failure and liver failure (Arbex et al., 2010). It should be used with caution in patients in the first trimester of pregnancy due to congenital abnormalities (Arbex et al., 2010).

2.5.1.10 Bedaquiline

Bedaquiline was the first new TB drug to be made available for treatment for more than 40 years for use in the treatment of MDR-TB (WHO, 2014). Bedaquiline (TMC207) is the first drug with a novel mechanism of action (DOH, 2013). It acts by inhibiting the *Mycobacterium tuberculosis* ATP synthase. There are already publications on its use inMDR/XDR-TB patients showing very promising results. In a phase IIb study in MDR-TB, the addition of TMC207 to a treatment regimen with second-line drugs versus placebo plus second-line drugs administered over 8 weeks showed sterilised sputum in 48% of the patients versus 9% for the placebo group (DOH, 2013). After 2 years of treatment, 815 of patients who received TMC207 plus the standard regimen were cured,as opposed to 575 of those who received only the standard regimen (DOH, 2013). It was granted accelerated approval by the United States Food and Drug Administration. Although it is still in Phase III trials, WHO urges caution in its use and strict adherence to the conditions listed in the WHO interim policy guidance. As part of efforts to improve outcomes for MDR/XDR-TB, 70 countries have started using bedaquiline (WHO, 2016). Below are the conditions listed by WHO for the use of bedaquiline (WHO, 2014).

Bedaquiline should be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol abuse. It must not be added alone to a failing regimen. An informed decision making-process by patients should be followed. Baseline testing and monitoring for QT prolongation and development of arrhythmia is imperative (WHO, 2014). Clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place. Spontaneous reporting of adverse drug reactions is reinforced at country level and active pharmacovigilance is established among patient groups treated with bedaquiline (WHO, 2014). In the absence of a specific drug-susceptibility test, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs). Resistance to other anti-TB drugs should be monitored, following WHO recommendations when bedaquiline is used in patients (WHO, 2014).

2.5.1.11 Delamanid

Delamanid is a new drug with a novel mechanism of action, which is now available for the treatment of adults with MDR-TB (WHO, 2014). The World Health Organization has revealed

that 39 countries had introduced delamanid by the end of 2015 to improve the outcomes of MDR/XDR-TB (WHO, 2016).Information about these new drugs remains limited, since it has only been through a phase llb trial, and studies for safety and efficacy. There are conditions that must be in place if delamanid is used to treat adults with MDR-TB. Below are the conditions listed by WHO for the use of delamanid (WHO, 2014).

- Delamanid should be used for a maximum duration of 6 months and at the suggested dosing: 400 mg daily for the first 2 weeks, followed by 200 mg 3 times per week for the remaining 22 weeks.
- Special caution is required when delamanid is used in people aged 65 and above. Also, caution is to be applied in adult patients living with HIV, patients with diabetes, hepatic or severe renal impairment and those who use alcohol or substances.
- Its use in pregnancy, breastfeeding is not advised but it can certainly be used in children (Harauz et al., 2017).
- Delamanid should be used along with four effective second-line drugs as well as PZA.
- It should not be used alone in a regimen in which the companion drugs are failing to show effectiveness.
- Pharmacovigilance measures should be in place to ensure early detection and proper management of adverse drug reactions and potential interactions with other drugs.
- Patients should be fully aware of the potential benefits and harms of delamanid and give informed consent before embarking on the treatment.

2.6 Drug-Drug interactions

The administration of two or more drugs simultaneously to the same patient can alter the absorption, distribution, hepatic metabolism and renal elimination of the drugs involved.

2.6.1 Drug interaction during absorption

Drug absorption is the movement of drug molecules from the site of administration into systemic circulation (Peloquin, 2002). Interactions between two drugs or between food or drinks and drugs can happen when they interfere with each other's absorption. The absorption rate of a drug may be increased or decreased by the pH of the medium around the site of absorption and the acid dissociation constant (pka) of the drug. For example, the absorption rate of weak acidic drugs will be higher in the stomach where the pH is acidic, as opposed to the alkaline pH in the

small intestine. The absorption rate of a weak basic drug will be increased in the small intestine, where the pH is alkaline (Brunton et al., 2011). The poor absorption of anti-TB drugs results in sub-therapeutic plasma concentration levels and treatment failure of such drugs, with increased risk of acquired drug resistance (Gurumurthy et al., 2004).

2.6.2 Drug interaction during distribution

The ability of a drug to produce the required pharmacological effect may be influenced by the extent to which the drug binds to proteins within the blood plasma. Drug–protein binding is reversible and equilibrium is established between the bound and unbound drug, regardless of the extent of protein binding. The less bound a drug is, the more effective it is, since it can cross cell membranes.Normally, it is the unbound fraction of a drug that exhibits pharmacological effects.
If both drug A and drug B are highly protein bound (>90%) and are given at the same time, they will both compete for protein-binding sites. If drug A is more competitive, it might displace drug B from the binding sites, increasing drug B's unbound fraction. This may increase the effects of drug B. This change in pharmacological effect could have adverse effects on the patient (Bruntonet al., 2011).

2.6.3 Hepatic drug metabolism

Drug metabolism mediated by the CYP450 system mainly occurs in the liver. Therefore, any dysfunction of the liver may lead to changes in drug metabolism. Drugs metabolised by the CYP450 system can be classified as cytochrome P450 substrates, inhibitors or inducers. Efavirenz, an ARV, is metabolized by CYP450. It is a 3A4 inducer and inhibitor and therefore interacts with other drugs administered concomitantly (Almond et al., 2005). Inhibition of CYP450 is usually reversible and competitive, such that the substrate and inhibitor compete for the same site on the enzyme. Drugs that inhibit CYP450 can cause reduced clearance and therefore increased plasma concentrationand therapeutic effect of drugs metabolised through the CYP450 enzyme system. Drugs that induce the CYP450 system increase the rate of liver metabolism. Induction of the CYP450 pathway then leads to increased clearance and a

subsequent fall in the plasma concentration and effectof drugs metabolised by the pathway (Tang et al., 2005).

2.6.4 Renal elimination

Drug–drug interactions at the renal level can involve several mechanisms. For example, reduced plasma binding leads to an increase in the excretion of highly bound drugs through an increase in glomerular filtration (Bonate et al., 1998).

In addition, the pH of urine and pka of the drug can influence the extent of the passive reabsorption of the drug in theproximal tubule. This mechanism is clinically significant for drugs that are excreted unchanged and have a narrow therapeutic index, such that changes in urine pH can interfere with plasma concentration. For example, the acidification of urine pH can increase the rate of passive reabsorption of weak acidic drugs, resulting in an increase in the half-life of the drug and therefore increased risk of drug interaction. Similarly, the alkalinisation of the urine pH can increase the rate of passive reabsorption of weak basic drugs, resulting in the increased plasma concentrations of the drug and consequently increased risk of drug interactions(Brunton et al., 2011).

The most notable mechanism of renal drug interaction is alteration of tubular active transport. Many drug transporters are actively responsible for the secretion and reabsorption of drugs in the kidney (Keith, 2006). Transporters are specific and are susceptible to competitive drug–drug interactions.

Competition between two drugs for the same transporter protein inhibits the renal clearance of one of the drugs and this results in the increased plasma concentration of the other drug that is a substrate of the transporter. In several cases, this increased plasma concentration can lead to increased toxic levels of the drug. For example, the inhibition of transporter organic anion transporting polypeptide by trimethoprim decreases lamivudine excretion into the proximal tubule, resulting in the increased plasma exposure of lamivudine (Taft, 2009).

2.6.5 Interaction between second-line anti-tuberculosis drugs and antiretroviral drugs

Due to the susceptibility of HIV-infected individuals to several opportunistic infections, they normally take a wide variety of drugs, in addition to their ARV therapy (De Maat et al., 2003). HIV positive patients taking ARVs and co-infected with TB have an additional problem of drug-drug interaction. For example, non-nucleoside reverse transcriptase inhibitors and protease inhibitors are metabolized by CYP450 and there is a significant PK drug interaction when they are administered concurrently with other drugs metabolized via the same enzyme pathway (Burma et al, 1999; De Mat et al., 2003). Therapeutic drug monitoring (TDM) should therefore be used to establish the adequacies of anti-TB drugs doses and ARV drug doses, particularly protease inhibitors [PIs} and non- nucleoside reverse transcriptase inhibitors (NNRTls) (Peloquin, 2002).

Furthermore, HIV-infected patients have a tendency to be more susceptible to adverse reactions such as peripheral neuropathy, cutaneous reactions, renal toxicity and gastro-intestinal disturbances (Weyer, 2005). A study has shown that there is an increased risk of peripheral neuropathy with concurrent use of ethambutol, ethionamide or isoniazid with stavudine or didanosine (Swart and Jones, 2009). Although stavudine and didanosine are no longer used in clinical practice. These patients should be monitored carefully and appropriate prophylaxis or treatment given simultaneously. Although there is scanty evidence to propose this, zidovudine may decrease levels of PZA (Swart and Jones, 2009). According to Kenyon et al (2011), a substantial proportion of patients taking tenofovir may develop certain of the features of Fanconi's syndrome (a proximal tubular wasting syndrome as a result of proximal convoluted tubular cells dysfunction).

Tenofovir may also cause renal failure. A recent report has revealed that tenofovir is associated with mild decreases in glomerular filtration rate (GFR) when compared with patients on other ARVs (National Department of Health, 2010). Ethionamide has been shown to cause depression, anxiety and psychosis when administered concurrently with efavirenz. These effects are commonly experienced in the first week of efavirenz therapy (Coyne et al., 2009).

Studies demonstrating interactions between second-line drugs that are used in MDR-TB treatment regimens and ARVs are very scanty, although the potential for adverse interactions is considerable. Therapeutic drug management (TDM) of drugs used in TB management is

supported, with TDM helpingtowards better control of TB treatment, particularly in patients co-infected with HIV and managing anti-TB drugs interactions (Peloquin, 2002). Routine therapeutic drug monitoring (TDM) is not possible in most low- and middle-income countries where MDR-TB is most prevalent.

2.6.6 Interaction between second-line anti-tuberculosis drugs and other drugs other than antiretroviral drugs commonly used in HIV-infected patients

It has been noted that terizidone can increase the serum levels of phenytoin and oral anticoagulants, as well as decreasing those of pyridoxine (Arbex et al., 2010). In patients using anticonvulsants and neuroleptics, the dose of terizidone should be adjusted. However, due to the potential effect that terizidone has on the central nervous system, patients should be closely monitored for side-effects of this drug combination. Arbex et al (2010) reported that the concomitant use of terizidone and fluoroquinolones could worsen the potential effects of terizidone on the central nervous system.

The ototoxity and nephrotoxicity of aminoglycosides can be potentiated when administering amphotericin B, vancomycin, cephalosporin, cisplatin and loop diuretics such as furosemide concurrently with aminoglycosides (Arbex et al., 2010). In addition, concomitant administration of aminoglycosides and neuromuscular blocking agents can cause respiratory depression, and patients with conditions such as myasthenia gravis, hypocalcaemia, severe hypokalaemia or hypomagnesaemia are susceptible to such side effects (Arbex et al., 2010).

According to Arbex et al (2010), the concomitant use of ethionamide and terizidone can potentiate these neurotoxic effects (hallucinations, irritability, tremors, depression, convulsions, psychosis, and peripheral neuropathy). There is a possible risk of drug interactions when administering ethionamide and para-aminosalicylic acid simultaneously as this can increase hepatotoxicity and the possibility of hypothyroidism (Arbex et al., 2010).

The concomitant administration of fluoroquinolones and nonsteroidal anti-inflammatory drugs (NSAIDS) could increase central nervous system stimulation and the possibility of convulsions.

In addition, vitamin supplements containing zinc or iron have been found to interfere with the gastrointestinal absorption of fluoroquinolones (Arbex et al., 2010). Fluoroquinolones can inhibit numerous cytochrome P450 sub-families, which increases the plasma concentrations of drugs that are metabolized via the cytochrome P450 system. It has also been noted that fluoroquinolones increase the serum levels of theophylline, glibenclamide and cyclosporine, as well as increasing the effect of oral anticoagulants (Coyne et al., 2009). Yew (2000) found that antacids containing calcium, aluminium, or magnesium interfere with the absorption and concentration of fluoroquinolones. According to Arbex et al (2010), fluoroquinolones should not be administered until 2 hours after the use of antacids, since probenecid and cimetidine can increase the serum levels of fluoroquinolones.

2.7 Drug food interactions

2.7.1 Interaction between second line anti-tuberculosis drugs and food

Food can affect the rate of absorption of a drug taken simultaneously, thus affecting the bioavailability of the drug. Grapefruit has been found to interfere with drugs that undergo CP450 oxidative metabolism in the intestinal wall or liver. It interferes with these drugs by binding to the iso- enzyme, CYP3A4, as a substrate and impairs first-pass metabolism through the inhibition of CYP3A4; the result is an increase in the bioavailability of these drugs and an increased risk of serious side effects (Leucuta and Nlase, 2006).

Chigutsa and colleagues describe the pharmacokinetics of an 800 mg oral dose of ofloxacin in adults with MDR-TB in 2 locations in South Africa. They found that the administration of ofloxacin with a meal resulted in delayed absorption (Chigutsa et al., 2012). According to Arbex et al (2010) foods, with the exception of dairy products with a high concentration of calcium, do not interfere with the absorption of ofloxacin, levofloxacin, or moxifloxacin, as they do with the absorption of other fluoroquinolones. Patients using ciprofloxacin should be instructed to avoid excessive use of foods with high caffeine content, since ciprofloxacin inhibits the cytochrome P450 system, thereby reducing caffeine clearance.

According to Arbex et al (2010),food increases the absorption of para-aminosalicylic acid. Para-aminosalicylic acid could be administered with water, orange juice, or fatty foods. Foods increase the time required for terizidone to be absorbed by 3.5 times, and there could be a 35% reduction in the maximum concentration of the drug (Arbex et al., 2010). Orange juice (and probably other acidic beverages) reduces the maximum concentration of the drug by 15%. Whenever possible, the drug should be ingested with water, well before or after meals.

2.7.2 Influence of disease on the pharmacokinetics and pharmacodynamics of second-line anti-tuberculosis drugs

Diseases can cause modifications in some organs (e.g. liver, kidneys), which would affect the pharmacokinetics of drugs. Conditions affecting the gastro-intestinal tract, liver, heart and kidneys may increase or decrease the PK of drugs used for the treatment of MDR-TB by altering their disposition, metabolism and elimination. Some of these conditions are gastro-enteritis, diarrhoea, malabsorption syndromes, hepatitis, and cirrhosis of the liver, congestive cardiac failure, renal failure and HIV infection (Yew, 2002).

The most important aspect of drug-disease interactions is malabsorption of anti-mycobacterial agents due to HIV enteropathy and other HIV-associated opportunistic infections of the gut (Yew, 2002). Rifabutin, a drug with equivalent anti-tuberculous activity in patients with HIV, appeared to be less frequently malabsorbed in this patient population compared with rifampicin (Yew, 2002).

Furthermore, it has been suggested that patients infected with HIV, with or without diarrhoea, may not sufficiently absorb anti-TB drugs. The study published by Gurumurthy et al (2004) reported that HIV-infected patients with or without TB had lower plasma concentrations of RIF and INH well below the therapeutic range. It was further stated that malabsorption of pyrazinamide and ethambutol was evident in HIV-positive patients co-infected with TB when compared to HIV-infected patients without TB (Gurumurthy et al., 2004). Some studies have

suggested that malabsorption of anti-tuberculosis drugs occurs in HIV-infected patients with advanced HIV infection (Patel et al., 1995; Berning et al., 2003; Gurumurthy et al., 2004). This resulting lower anti-TB drug exposure may lead to acquired drug-resistance and the reduced efficacy of anti-TB therapy in patients infected with HIV (Gurumurthy et al., 2004).

2.8 Treatment outcomes, and factors influencing drug-resistant TB treatment outcomes

2.8.1 Treatment outcomes of multidrug-resistant tuberculosis

Treatment outcomes of MDR-TB are poor when compared to-drug sensitive TB. The estimated success rate of drug sensitive TB and MDR-TB was 83% and 48% in 2015, respectively (WHO 2016). Systematic reviews and meta-analysis results based on data from different continents and over 21 countries have revealed a successful MDR-TB treatment outcome of about 62-64% (Johnston et al., 2009; Orenstein et al., 2009). These studies defined successful treatment as a combination of cure and 'treatment completed', based on the WHO classification of treatment outcomes. Both studies reported similar levels of outcome in terms of failure (6-8%), default (12-13%), died (11%) and transferred out (2%) (Johnston et al., 2009; Orenstein et al., 2009).

A recent large individual patient data meta-analysis, consisting of 9153 patients, documented a very low proportion of treatment success, which was slightly more than half of the patient population (54%) compared to other treatment outcomes (Ahuja et al., 2012). These investigators utilised data from three systematic reviews (Johnston et al., 2009; Orenstein et al., 2009; Akcakira 2010). The failure/relapsed rate and default rate in the study were 8% and 23% respectively. The proportion of patients who died in the study was 15% and these were mainly older HIV-positive patients. The researchers revealed that patients who defaulted on treatment were more likely to be older people.

In South Africa, 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 outcomes in HIV-positive patients prior to

the scaling up of Antiretroviral therapy (Shean et al., 2008; Brust et al., 2010; Gandhi et al., 2010 Farley et al., 2011). These studies conducted in South Africa revealed much lower and poorer treatment success rates of about 43-46%, with higher and earlier mortality rates of over 23%, especially among HIV-positive patients (Farley et al., 2011) –a higher default and treatment failure rate using a standardized treatment regimen when compared to the meta-analyses (Johnston et al., 2009; Orenstein et al., 2009) which used more studies with individualised treatment regimens than the standardised regimen.

A recent study conducted in South Africa reported a cure rate of 36% in MDR-TB patients (Mugabo et al., 2015). The MDR-TB cure rates reported at national level range between (30-50%) in patients without HIV–infection in South Africa (DOH, 2013). Mugabo et al. (2015) reported a cure rate of 36% in HIV-positive and 35% in HIV-negative patients with MDR-TB. Another study conducted in South Africa by Farley et al (2011) reported a cure rate of 40% in HIV-positive patients and 49.6% in HIV-negative patients. Another recent study conducted in South Africa reported a cure rate of 29% in HIV-positive patients with MDR-TB (Umanah et al., 2015). These cure rates are poor in patients with MDR-TB and factors influencing them need to be investigated.

Several researchers in South Africa have reported failure rates ranging between 2.5% and 17% among MDR-TB patients (Brust et al., 2010; Farley et al., 2011; Marais et al., 2013). Farley et al (2011) reported failure rates of 4.2% in HIV-positive and 13.2% in HIV-negative patients with MDR-TB. A recent study reported a failure rate of (9%) in HIV-negative patients with MDR-TB and (5%) in HIV-positive patients with MDR-TB (Mugabo et al., 2015). Other investigators from South Africa reported a default rate ranging between 20% and 29% (Shean et al., 2008; Farley et al; 2011; Marais et al., 2013). MDR-TB and HIV co-infection are amongst the condition-related factors reported as predictors of MDR-TB treatment default (Brust et al., 2010). However, other studies have found no link between HIV and MDR-TB treatment default rates (Shean et al., 2008; Farley et al., 2011). Farley et al (2011) reported no differences in the default rate between HIV-positive patients (20.6%) and HIV-negative patients (21.1%) with MDR-TB. A recent study reported a default rate of 20% and 25% in HIV-negative patients and HIV-positive patients with MDR-TB (Mugabo et al., 2015). A study conducted on the

evaluations of MDR-TB treatment default in South Africa revealed that healthcare workers' attitude and substance abuse are associated with patient default (Holtz et al., 2006).

2.8.2 Factors influencing treatment outcomes in multidrug resistant tuberculosis

Several investigators have reported high mortality and poor treatment outcomes associated with HIV-infected patients (Flament-Saillour et al., 1999; Ghandi et al., 2006, Wells et al., 2007; Kliiman and Altraja, 2009; Seung et al., 2009; Brust et al., 2010; Farley et al., 2011; Kurbatova et al., 2012). The poor outcomes and especially rapid time to death have mostly been observed in the absence of effective antiretroviral treatment (Gandhi et al., 2006; Wells et al., 2007; Seung et al., 2009). HIV-co-infected MDR-TB patients appear to benefit from antiretroviral treatment against HIV; however, simultaneous management of the treatment of both diseases is complicated. Although the combination of TB treatment and antiretroviral therapy can increase survival in HIV-TB co-infected patients in general, it is less likely to do so in patients with drug-resistant TB (Dheda et al., 2004; Holtz et al., 2006).

A study from the KwaZulu-Natal Province, the first extensive study detailing the treatment outcomes of MDR-TB patients in a TB referral hospital in South Africa, in 2010 reported an association between HIV co-infection and death. Although the study period was before the availability of ART therapy in the public sector (2000-2003), the authors attributed the HIV/death association to the lack of ART therapy and recommended an integration of ART with second-line anti-TB treatment in the management of MDR-TB patients (Brust et al., 2010). However,more recent studies have shown no association between HIV status and poor treatment outcomes,such as death (Loveday et al., 2012; Satti et al., 2012; Marais et al., 2013; Mugabo et al., 2015). These studies have shown that HIV-positive patients could achieve similar treatment outcomes with HIV-negative patients when treated concurrently with second line anti-TB drugs and antiretroviral therapy. However, the co-administration of ART together with MDR-TB treatment has notably improved treatment outcomes of MDR-TB patients in previous studies and the rapid occurrence of death that is often associated with HIV/MDR-TB co-infected patients is

greatly decreased with effective early treatment of both HIV and MDR-TB (Brust et al., 2011: Hafkin et al., 2013).

Several authors have reported previous anti-TB treatment as a risk factor for poor treatment outcomes such as failure and mortality in MDR-TB patients (Faustini et al, 2006; Johnston et al., 2009; Kliiman and Altraja, 2009; Brust et al., 2010). A meta-analysis study reported successful outcomes in new MDR-TB patients and poor treatment outcomes in patients previously treated for MDR-TB (Johnston et al., 2009). Another study conducted in South Africa by Dheda et al. (2010) found that previous treatment for MDR-TB was an independent predictor of poor treatment outcomes such as death. In contrast to the above studies, Marais et al (2013) found no association between previous TB treatment and poor treatment outcomes in MDR-TB patients. They also revealed that no association was found in the treatment outcomes between new versus retreatment MDR-TB cases. The previous history of TB suggests that this could possibly be due to the high rates of drug resistance, which could be regarded as the failure of TB control before 2000, due to inadequate case management, interruption of drug supply and use of inadequate drug regimens or defaulting treatment within recent years.

Another factor causing poor treatment outcomes in MDR-TB is treatment with too few drugs. Some researchers report that treatment with five drugs or fewer anti-TB drugs for 3 months or longer was associated with poor treatment outcomes such as mortality and failures in MDR-TB patients (Leimane et al., 2005; Umanah et al., 2015). Some researchers reported that patients resistant to 5 or more drugs were more likely to fail treatment (Brust et al 2010). They emphasize the need for more than 4 drugs in the treatment of MDR-TB.

According to Kliiman and Altraja (2009), several studies emphasize the important role of resistance to ofloxacin in poor MDR-TB treatment outcome. It was noted that the risk of poor treatment outcome was more than twice as high among patients in whom *Mycobacterium tuberculosis* had resistance to ofloxacin (Kliiman and Altrajah, 2009). Other studies have reported poor treatment outcomes in patients with fluoroquinolone resistance (Leimane et al., 2005; Johnston et al., 2009; Kurbatova et al., 2012). In contrast to this study, a treatment regimen containing ofloxacin has been found to be a predictor of successful treatment outcomes

in another study (Chiang et al., 2006). This finding further emphasizes the importance of ofloxacin in MDR-TB treatment regimens, and highlights the need for preserving susceptibility to ofloxacin, as well as pointing out the clinical value of ofloxacin resistance.

There are conflicting reports of gender as a predictor of treatment failure. Some researchers have shown that female sex is a predictor of treatment failure (Lockman et al., 2001; Mdivani et al., 2008; Marais et al., 2013). On the other hand, male sexhas also been associated with treatment failure, according to other reports (Johnston et al., 2009; Babalik et al., 2013). However, male gender was found to be associated with treatment failure and death in South Africa (Brust et al., 2010; Farley et al., 2011). Another study in South Africa reported poor treatment outcomes, such as death, in female sex (Marais et al, 2013), but this was a weak association observed between female sex and poor treatment outcomes in this study.

Another factor influencing poor treatment outcomes is that body mass index (BMI) of less than 18.5kg/m^2 as marker of poor nutritional status in patients with TB at treatment initiation has been described as a risk factor of poor treatment outcomes in some studies (Leimane et al., 2005; Kurbatova et al., 2012). A study conducted in Lesotho found a strong association between low BMI at baseline and increased risk of death or failure (Satti et. al., 2012). In addition, another study reported body weight of less than 45 and less than 60 kg to be associated with death and treatment failure (Farley et al., 2011). Another study conducted in South Africa reported severe underweight to be associated with mortality (Umanah et al., 2015).

Gandhi et al (2012) found an association between low CD4 cell count and mortality in MDR-TB patients. These authors reported that HIV-positive patients with a CD4 count less than 50 cells/$mm^3$and 51-200 cells/mm^3 were found to be associated with mortality. The impact of low CD4 count and higher drug resistance may be cumulative in individual patients, resulting in dramatic mortality in MDR-TB and XDR-TB patients. According to a report by Gandhi et al (2012), previous studies show that TB incidence and allcauses of mortality are both higher with low CD4 cell counts, and that risk diminishes as the CD4 cell count improves on ART. Some other studies have reported changes (decrease / increase) in CD4 count as a factor influencing the treatment outcomes in MDR-TB patients. They reported that patients whose CD4 count

decreased during treatment were more likely to fail treatment (Satti et al., 2012; Andries et al., 2013).

Extrapulmonary TB caused by multidrug–resistant isolates has been reported to be associated with poor treatment outcomes such as treatment failure and mortality (Gandhi et al., 2102; Kurbatova et al., 2012). Extrapulmonary disease in the setting of HIV infection signifies advanced immunosuppression, and there is a complex interaction between the cellular immune system, the invading *Mycobacterium*and anti-tuberculous agents (Sandman et al., 1999).

Another factor is the association between the genotype strain family of *Mycobacterium* and poor treatment outcomes. A study conducted in South Africa by Marais et al (2013) reported the entire strain of families to have similar rates of successful treatment outcomes, with the exception of the Haarlem (H) family, which was associated with death. This suggests that genotypic determination could potentially serve as a prognostic factor.

Studies assessing age as a risk factor for poor treatment outcomes in MDR-TB have yielded conflicting results. An association between advanced age and treatment failure has been demonstrated in studies (Vasankari et al., 2007; Babalik et al., 2013; Kurbatova, et al., 2012). This association between advanced age and treatment failure is related to increased comorbidity, overall physiological deterioration and difficulty in accessing several healthcare opportunities, along with increasing age (Vasankari et al., 2007; Babalik et al., 2013). Other studies conducted in South Africa and Lesotho have reported poor treatment outcomes such as treatment failure and death in the age group of 31-40 years and 40 years respectively (Seung et al., 2009; Brust et al., 2010).

Another study found that the presence of any additional disease and chronic lung disease was associated with adverse outcomes (Aysun et al., 2015). Vasankari et al (2007) reported that the presence of immunosuppression and malignity were associated with death. Other studies reported the presence of any comorbid disease, opportunistic infection, diabetes mellitus or malignity to be associated with poor outcomes such as failure and mortality in MDR-TB patients (Vasankari et al., 2007; Babalik et al., 2013; Umanah et al., 2015).

2.8.3 Treatment outcomes of Rifampicin mono-resistant TB

Treatment outcome of Rifampicin mono-resistant TB (RMR-TB) is poor when compared to drug-sensitive TB. Investigators from France and Europe have reported 67% and 70.8% cure rates in RMR-TB patients (Meyssonnier et al., 2014; Villegas et al., 2016). Several investigators have reported high mortality and failure associated with RMR-TB patients (Sandman et al., 1999; Mukinda et al., 2012; Prach et al., 2013; Schnippel et al., 2015; Villegas et al., 2016). A study conducted in France documented a 33% failure rate in RMR-TB patients (Meyssonnier et al., 2014).

A study from the Western Cape Province, the first extensive study detailing the treatment outcomes of RMR-TB patients in an MDR-TB referral hospital in South Africa in 2012, reported an association between RMR-TB and treatment failure (Mukinda et al., 2012). The authors attributed the treatment failure to the use of poor quality drugs previouslyused, and recommended that DOTS should be reinforced to increase treatment adherence. The authors further emphasized the need for drug sensitivity testing for HIV-coinfected patients.

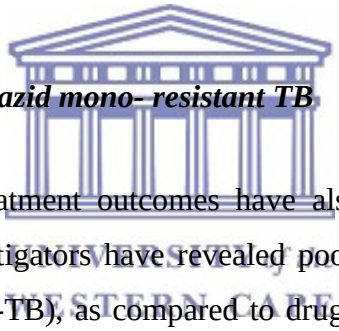
Another recent study conducted in South Africa reported a 33.7% cure rate in Rifampicin mono-resistant TB patients (Schnippel et al., 2015), but alsoa failure and unknown rate of 36.8% and 51.4% in RMR-TB patients (Schnippel et al., 2015). Another study from Europe reported a 20.83% unknown rate in RMR-TB patients (Villegas et al., 2016). Very scanty studies have been conductedon the treatment outcomes in RMR-TB patients.

2.8.4 Factors influencing treatment outcomes in Rifampicin mono-resistant TB

There have been conflicting reports of HIV infection causing poor treatment outcomes in Rifampicin mono-resistant TB patients. Studies have revealed that HIV infection was one of the factors causing poor treatment outcomes such as death and treatment failure in Rifampicin mono-resistant TB patients (Mukinda et al., 2012; Prach et al., 2013). Prach et al (2013) revealed that out of 74 patients with Rifampicin mono-resistant TB/co- infection with HIV, 31 (42%) died

during treatment. They concluded that patients with Rifampicin mono-resistant TB/ HIVco-infection were more likely to have poor treatment outcomes. However, other investigators in France revealed that HIV infection is not a factor influencing poor treatment outcomes in Rifampicin mono-resistant TB patients (Meyssonnier et al., 2014).

PreviousTB treatment had been reported as a factor influencing treatment outcomes in Rifampicin mono-resistant TB patients. Some researchers from France revealed thatpatients previously treated for RMR-TB were more likely to have unfavourable treatment outcomes, such as death and treatment failures, as compared to new patients (Meyssonnier et al., 2014). The authors reported a failure rate of 50% and 19% in previously treated RMR-TB patients and new RMR-TB patients respectively. They showed a link between poor treatment outcomes and retreatment cases in Rifampicin mono-resistant TB patients (Meyssonnier et al., 2014).



2.8.5 Treatment outcomes of Isoniazid mono- resistant TB

Isoniazid mono-resistance TB treatment outcomes have also been a topic of debate due to conflicting studies. Several investigators have revealed poor treatment outcomes in Isoniazid mono-resistant TB patients (HMR-TB), as compared to drug-sensitive TB patients (Menzies et al., 2009; Prach et al., 2013; Villegas et al., 2016). Several researchers from the United States of America and Europe have reported treatment success ranging between 56% and 74.1% in HMR-TB patients (Gegia et al., 2012; Lee et al., 2015; Villegas et al., 2016).A study conducted in South Africa reported a 65% successful treatment rate in HMR-TB patients. (Jacobson et al., 2011)

Several studies have revealed that Isoniazid mono-resistant TB is associated with worse treatment outcomes and frequently associated with a high rate of treatment failure and mortality (Menzies et al., 2009; Jacobson et al., 2011; Gegia et al., 2012; Villegas et al., 2016). Although the treatment outcomes for Isoniazid mono-resistant TB patients are poor compared to patients with drug-susceptible TB, successful outcomes have been reported in other studies (Cattamanchi et al., 2009; Wang et al., 2014). Cattamanchi et al (2009) retrospectively reviewed all cases of

culture-confirmed, Isoniazid mono-resistant TB reported during a 14-year period (1992- 2005) in the United State of America, and compared them with a time-matched sample of drug-susceptible tuberculosis cases. They reported that the treatment outcomes for patients with Isoniazid mono-resistant TB were excellent and were no different from the drug-susceptible cases.

According to a global meta-analysis study of outcomes among patients with Isoniazid mono-resistance, poor treatment outcomes, with a failure rate ranging from 18% to 44%, were reported (Menzies et al., 2009). Several other researchers also failed to prove an association between Isoniazid mono-resistant TB and treatment failure. These studies from the United States of America and Europe reported failure rates ranging between 2%-8% in HMR-TB patients (Cattamanchi et al., 2009; Bang et al., 2010; Villegas et al., 2016).

Other investigators in South Africa, who conducted a study on the treatment outcomes of Isoniazid mono-resistantTB patients, reported a failure rate in 16% of the cohort, 66% of the cohort progressed to MDR-TB and 16% defaulted on treatment (Jacobson et al., 2011). A study from the United States of America reported a default rate of 20.6% in HMR-TB patients (Gegia et al; 2012). Another study from Europe documented an 18.82% unknown rate in HMR-TB patients (Villegas et al., 2016).

2.8.6 Factors influencing treatment outcomes in Isoniazid mono- resistant TB

Researchers have reported previous anti-TB treatment as a risk factor for poor treatment outcomes such as failure and mortality in Isoniazid mono-resistant TB patients (Gesia et al., 2012; Wang et al., 2014). A study by Gegia et al (2012) reported an association between previous TB treatment history and treatment failure. They reported that previously treated patients with HMR-TB were more likely to have unfavourable outcomes, as compared to new HMR-TB patients. A recent study reported that Isoniazid resistance of any type in both new and retreatment cases were associated with failure (Lee et al., 2015). In contrast to the above studies, no association was found between previous TB treatment and poor treatment outcomes in HMR-TB patients in a study conducted in South Africa (Jacobson et al., 2011). A study conducted in

the United States of America revealed that patients with a history of previous TB treatment were more likely to default from treatment, particularly when given a regimen of a longer duration (Gegia et al., 2012). The authors reported the probability of successful outcomes of 76% in new and 58% in previously-treated patients with HMR-TB.

Studies assessing age as a risk factor for poor treatment outcomes in Isoniazid mono-resistant TB have yielded conflicting results. An association between advanced age of >65 years and treatment failure or death has been demonstrated in studies (Gegia et al., 2012; Chien et al., 2015). In a study conducted in South Africa, the first study on the treatment outcomes of Isoniazid mono-resistant TB patients reported that patients between 33 years and 43 years had worse treatment outcomes, as compared to patients between 44 years to 65 years (Jacobson et al., 2011). The authors concluded that poorer compliance and default were the reason why the treatment outcomes were worse in this group of patients. They further revealed that HIV infection and new cases did not predict worse outcomes in this study. Some groups of researchers have shown that male sex is a predictor of treatment failure or death in Isoniazid mono-resistant TB patients (Chien et al., 2015). However, there was no link between sex and poor treatment outcomes in a study conducted in South Africa (Jacobson et al., 2011).

Other factors associated with poor outcomes in Isoniazid mono-resistant TB patients documented by researchers were smoking, Isoniazid resistance, cancer (underlying malignancy), liver cirrhosis, rifampicin interruption during treatment, and smear-positive cases (Jacobson et al., 2011; Chien et al., 2015).

2.8.7 Treatment outcomes in MDR-TB/HIV co-infected patients based on ART duration and 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 (Issakidis et al., 2011; Palacios et al., 2012; Mugabo et al., 2015; Umanah et al., 2015). Palacios et al (2012) noted a lower

death-rate in HIV-positive patients who had started antiretroviral therapy early compared to those who were not on ART. The authors reported that 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 et al (2001), who compared mortality in MDR-TB HIV-positive patients prior to the availability of Highly Active Antiretroviral Therapy (HAART) and during the HAART era. These studies did not consider the 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 favorable outcomes in terms of longer median survival time (Satti et al., 2012). Satti et al (2012) reported no association between HIV-positive patients who commenced ART prior to or after MDR-TB treatment. They reported that the time to death in HIV-positive patients who were not already on ART prior to MDR-TB treatment was significantly shorter compared to HIV-positive patients who were already on ART.

A recent study conducted in South Africa reported a cure and failure rate of 35% and 65% in HIV-positive patients with MDR-TB on ART (Mugabo et al., 2015). The authors reported that there were no differences in the treatment outcomes between HIV-positive patients receiving ART and HIV-positive patients not on ART. Another recent study conducted in South Africa reported a 33.4% cure rate, a 2.9% failure rate, a 21.8% death rate, a 4.8% transferred out rate, a 19.3% default rate, a 16.9 completed rate and 0.9% were still on treatment in HIV-positive patients with MDR-TB on ART before the commencement of MDR-TB treatment (Umanah et al., 2015). The authors reported significant association with higher mortality among patients who commenced ART before initiating MDR-TB treatment, when compared with ART initiation after commencement of MDR-TB treatment. These authors pointed out the importance of early initiation of ARVs and their protective benefits for HIV.ART has been shown to confer a protective effect on mortality in HIV-positive patients on MDR-TB treatment (Palacios et al., 2012), and this evidence supports the current WHO guidelines on commencing ART within 2-8 weeks after commencement of MDR-TB, irrespective of the CD4 count (WHO, 2011), compared to that which was in operation prior to 2010, when ART was initiated in patients with CD4 cell count less than 350 cells/mm^3.A previous study conducted in South Africa has shown that

receiving ART was not associated with improved survival in HIV-infected MDR-TB patients (Ghandi et al., 2012). But Isaakidis et al (2011) reported improved overall outcomes, with an increase in the median CD4 count (after one to two years of treatment) of HIV co-infected patients, the majority of whom were on ART before initiation of MDR-TB treatment. Hence, adequate data is needed in South Africa on the outcomes of MDR-TB in HIV-positive patients who initiated ART before the commencement of MDR-TB treatment, compared to those who commenced ART afterwards, to support the timely initiation of ART and improve the overall outcomes of MDR-TB in HIV-positive patients.

2.9 Microbiological parameters and pharmacotherapeutic parameters in patients with drug-resistant tuberculosis

Researchers from Lesotho, South Africa and Botswana, Seung et al (2009), Brust et al (2011) and Hafkin et al (2013) respectively, have described the influence of HIV infection on the time to sputum culture conversion in MDR-TB patients at the end of the intensive phase of treatment. These three studies reported that HIV infection does not affect the time to sputum culture conversion. The median time to sputum culture conversion in HIV-positive and HIV-negative MDR-TB patients in two of the studies were as follows: HIV-positive 54 days (IQR 41-90) and HIV-negative 103.5 days (IQR 86-116), and 78 days (IQR 42–186 days) for HIV-positive and 95 days (IQR 70–133) for HIV-negative patients respectively (Brust et al., 2011; Hafkin et al., 2013)

These studies from Southern Africa have demonstrated high rates of culture conversion among HIV-infected individuals who survived during anti-tuberculosis treatment. Together they include fewer than 50 HIV-infected patients, and only the study from Lesotho reported worse survival rates among HIV-infected individuals. Another study conducted in Taiwan during an 8-year period (2004- 2011) documented worse treatment outcomes, despite early sputum culture conversion in HMR-TB patients (Chien et al., 2015). It was revealed by the authors that 68.7% had poor treatment outcomes.

Another investigator, who conducted a study in Latvia for non-HIV-infected patients, reported a median time of 60 days (range of 4 to 462 days) in patients (Holtz et al., 2006). They

investigated the influence of sputum culture reconversion and revealed that patients who were previously treated with second-line drugs were more likely to revert after achieving initial sputum culture conversion.

Very few studies have determined the sputum culture conversion time in RMR-TB patients. A study conducted in the United States of America reported culture conversion to be longer in patients with RMR-TB as compared to drug sensitive TB (Prach et al., 2013).The median time to sputum culture conversion reported by the authors was 93.5 days (IQR 42.0-162.0) in RMR-TB patients and 50 days (27.0–81.0) in drug sensitive TB cases. This study from the United States of America, have demonstrated high rates of culture conversion among RMR-TB patients who survived during anti-tuberculosis treatment.

Limited studies have been conducted on the time to sputum clearance in HMR-TB patients. A study conducted in the United States of America has shown that culture conversion time can be almost similar between patients with Isoniazid mono-resistant TB (HMR-TB) and patients with drug sensitive-TB (Prach et al., 2013). The investigators reported a median time of 48 days (IQR 26-84) in HMR-TB patients and 50 days (27.0–81.0)in drug- sensitive TB patients. Studies from the United States of America, have demonstrated high rates of culture conversion among HMR-TB patients who survived during anti-tuberculosis treatment (Prach et al., 2013; LoBue and Moker, 2005).

CHAPTER THREE: METHODS

3.1 Study design

This study was designed as a retrospective observational study that assessed the influence of microbiological parameters on DR-TB treatment outcomes. The microbiological parameters assessed include: HIV-infection, sputum culture conversion time, immunological and virological profile, antiretroviral therapy, the impact of inappropriate (i.e. low and high) anti-tuberculosis drug dose on the time to sputum culture conversion (reference anti-TB drug dose in Table 1, Table 2 and section 3.8which were used to identify patients with inappropriate anti-TB drug dose), drug resistance (comparing mono-resistance-TB cases and MDR-TB cases), the replacement of ofloxacin by moxifloxacin in DR-TB treatment regimen and DR-TB localization.

3.2 Data collection site

The study data was collected at the Brewelskoof Hospital. This hospital operates in the Worcester/Robertson health District of the Cape Winelands, South Africa.

3.3 Study Population

The study population includes male and female patients, HIV-positive and HIV-negative, 18 to 65 years old, with confirmed MDR-TB and mono-resistance TB (RMR-TB and HMR-TB) who started and finished treatment between 2009- 2015.

3.4 Inclusion and exclusion criteria:

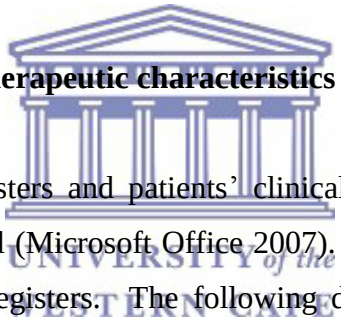
Inclusion criteria were sputum microbiology, culture and sensitivity at baseline and every month during treatment. Recordsof any of the following treatment outcomes cured, completed, failed,

died or transferred out. Immunological and virological profile at baseline, six, twelve, and twenty-fourmonths after starting anti-TB treatment.

Exclusion criteria were MDR-TB patients without a definitive treatment outcome, patients with no evidence of MDR-TB, patients with no monthly sputum culture result, Pre-XDR-TB patients, XDR-TB patients, patients of less than 18 years and more than 65 years.

3.5 Anti-tuberculosis medication used at Brewelskoof Hospital

The drugs used for the treatment of DR-TB patients at Brewelskoof Hospital involve a combination of the following first and second line drugs: ethambutol, pyrazinamide, isoniazid, rifampicin, ofloxacin/moxifloxacin, ethionamide, kanamycin and terizidone.



3.6 Demographics, clinical and therapeutic characteristics of all patients

Data was collected from TB registers and patients' clinical records. All data collected was entered into a database using Excel (Microsoft Office 2007). Adata-collection form was used to extract data from health-facility registers. The following data were extracted from patients' records: year of registration, sex, age, patient's diagnostic category, treatment regimen and doses, DR-TB confirmatory, final treatment outcomes, smear microbiology, culture and sensitivity (MCS) test results, HIV-status, TB and DR-TB localization, TB history, anti-retroviral therapy history, CD4 count, viral load, monthly sputum MCS and sputum culture conversion date.

3.7 Data Collection

All patients involved in the study were identified by searching the TB register and patient's folder for first and second-line susceptibility test results. These results were screened during data collection/data cleaning to remove duplicates and only the first known MDR-TB and mono-resistant TB data for each patient were selected for use in the study. The patients' data included in the study exhibited one of fourdrug-resistance profiles:resistance to isoniazid only, resistance

to rifampicin only, resistance to isoniazid and rifampicin only, resistance to isoniazid, rifampicin and streptomycin or ethambutol. The current study data reflects resistance patterns to first-line anti-TB drugs. Patients who were resistant to 2 or more second-line drugs were not included in the study.

3.8 Dosage of anti-TB drugs (DOH, 2013)

Dosages of anti-TB drugs prescribed to drug-resistant TB patients in this study were compared with dosages recommended by the national Department of Health (South Africa) Guidelines for the diagnosis and treatment of drug-resistant-TB patients (Table 1,Table 2, and sections 3.8.1 and 3.8.2).

3.8.1 Dosing of Isoniazid in single-drug preparation

DOH recommended 150 mg for patients weighing less than 33 kg, 400 mg for patients weighing 33-50 kg, 450 mg for patients weighing 51-70 kg and 600 mg for patients weighing >70 kg (DOH, 2013).

3.8.2 Dosing of Ofloxacin in single-drug preparation

DOH recommended 600 mg for patients weighing less than 33 kg, 600 mg for patients weighing 33-50 kg, 800 mg for patients weighing 51-70 kg and 800 mg for patients weighing >70 kg (DOH, 2013).

3.9 Validity and reliability of data collected

The patient's folder and TB register were made available by the sister in charge of DR-TB data records. Any patient in the database who had a result showing genotypic mono-resistant TB to rifampicin and isoniazid was included. Conversely, in those with no results for either rifampicin or INH resistance, the patient's information was excluded. Duplicate entries were removed from the data, and patients less than 18 years of age and more than 65 years old were excluded.

3.10 Definitions of commonly-used terms in the study

Terminologies for drug-resistant tuberculosis treatment

The following definitions were recommended by the World Health Organisation (WHO, 2013) and updated in WHO, 2014 report.

Case of tuberculosis

Case of tuberculosis refers to a patient in whom tuberculosis has been bacteriologically confirmed, or has been diagnosed by a clinician using other methods of diagnosis.

Pulmonary tuberculosis

Pulmonary TB is defined as any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as pulmonary TB because there are lesions in the lungs.

Extrapulmonary tuberculosis

Any bacteriologically-confirmed or clinically-diagnosed case of TB involving organs other than the lungs is known as extrapulmonary TB e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

New case of TB

A patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month.

Retreatment case of TB

There are three types of retreatment case:

(i) A patient previously treated for TB. Previously treated patients who have received 1 month or more of anti-TB drugs in the past or who have started on a retreatment regimen after previous treatment has failed (treatment after failure).

(ii) Treatment after loss to follow-up patients previously treated for TB and declared lost to follow-up at the end of their most recent treatment episode. (These were previously known as

"treatment after default" patients).

(iii) Relapse patients are those previously treated for TB, declared cured or treatment completed at the end of their most recent treatment episode and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing in clinical isolates confirmed to be *Mycobacterium tuberculosis*:

- Monoresistance: resistance to one first-line anti-tuberculosis drug only.
- Rifampicin mono-resistant TB (RMR-TB): Rifampicin mono-resistant TB which is resistant to Rifampicin alone (WHO, 2015),
- Isoniazid mono- resistant TB (HMR-TB): resistantonly to Isoniazid (WHO, 2015).
- Multidrug resistance (MDR-TB): resistance to at least isoniazid and rifampicin, the two most powerful first-line anti-TB medicines (WHO, 2016).
- Extensive drug resistance (XDR-TB): MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable agent (WHO, 2016).

Standard definitions of DR-TB outcomes

Treatment outcomes were defined using World Health Organization categories(WHO, 2013):

- 'Cure': Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

- 'Treatment completed' as recommended by the national policy without evidence of failure, but no record that three or more consecutive cultures taken at least 30 days apart are negative.

- ‘Treatment failed’: Treatment terminated or need for permanent regimen change of ≥2 anti-TB drugs because of lack of conversion in the continuation phase, or bacteriological reversion* in the continuation phase after conversion* to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs).

- ‘Death’: patient who dies for any reason during the course of treatment.

- ‘Lost to follow up’: patient whose treatment was interrupted for 2 consecutive months or more (this category was previously known as ‘defaulted’).

- ‘Not evaluated’: A patient for whom no treatment outcome is assigned. This includes cases ‘transferred out’ to another treatment unit and whose treatment outcome is unknown.
- ‘Sputum culture conversion’ is defined as two consecutive negative cultures taken at least 30 days apart after initiation of MDR-TB therapy. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

- ‘Sputum culture reconversion to positive’: Cultures are considered to have reverted to positive when after initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. For the purpose of defining ‘Treatment failed’, reversion is only considered when it occurs in the continuation phase.

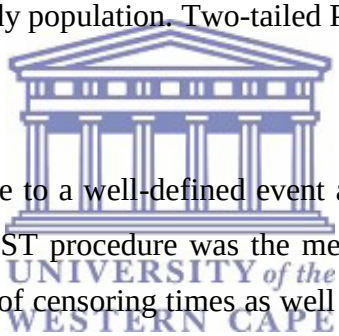
- Poor treatment outcomes: are outcomes such as died and failure.

DR-TB outcomes were defined using the standard definitions recommended by WHO. Treatment outcomes were: cured, treatment completed, failed, defaulted, transfer and death. Theseare further categorized into the following in this study: cured, not cured (completed, died and failed) and unknown (defaulted and transferred out).

3.11 Statistical analysis of data

The data collected during the study was organized and coded into data collection forms anonymously before being capturedby Microsoft Excel. Analysis was done using SAS version 9.0.

Basic statistics such as mean, standard deviation, median and range were used to describe continuous and ordinal variables, and frequency tables for nominal variables. When data was not normally distributed, the Wilcoxon Rank Sum test, the non-parametric alternative to a paired t-test, was used and the time to culture conversion were reported as median and range. The Kruskal-Wallis one-way analysis of variance was used in comparing more than two groups to see if they originate from the same population. Statistical significance was assumed at the p-value <0.01 significant level to avoid a false positive**.** The p-value <0.01 was used to avoid too many type 1 error and also due to the study population. Two-tailed P- value was reported.



Sputum conversion time is the time to a well-defined event and can be analysed using survival analysis methods. The ICLIFETEST procedure was the method used in the survival analysis. These methods require knowledge of censoring times as well as actual times to the event. There were cases where patient's sputum did 'not convert' or censored. Censoring time was found based on the algorithm (a gap of 2 or more would determine the censoring time). Patients whose sputum cultures did not convert due to death or failure were described, but were right-censored from the primary analysis.

3.12 Ethical considerations

This study was registered and approved by the University of the Western Cape Ethics Committee under the ethics clearance registration number 07/6/12. Permission to access patients' information was granted by the Provincial Department of Health, as well as the medical superintendent of Brewelskoof Hospital. The study was conducted according to the Helsinki and ICH guidelines. Patient information was captured anonymously, and all the data obtained were treated as confidential.

3.14 Dissemination of research results

The study results will be disseminated through the following channels:

a. Presentation at Department, School of Pharmacy, University of Western Cape
b. Conference presentations
c. Publication in scientific journals
d. Thesis for Master's degree at the university

CHAPTER FOUR: RESULTS

4.1 Patient's demographics and clinical characteristics

This study describes the treatment outcomes of 386 drug-resistant TB patients(57.5% males and 42.% females), which includes 244 (63.2%) MDR-TB patients, 103 (26.%) Rifampicin mono-resistant TB (RMR-TB) patients, and 39 (10.1%) Isoniazid mono-resistant-TB (HMR-TB) patients.

4.1.1 MDR-TB patients

Out of 244 (63.2%) MDR-TB patients, 146 (59.8%) and 98 (40.%) were male and female respectively. One hundred and ninety (77.%) patients had previously been treated with anti-TB drugs. Two-hundred and twenty-seven (93.0%) patients were infected with pulmonary TB, 13 (5.3%) patients were infected with extrapulmonary TB and only 4 patients (1.6%) were co-infected with pulmonary and extrapulmonary TB. Fifty- four (22.1%) patients were new cases of MDR-TB and 190 (77.%) patients were retreatment cases. Amongst the retreatment cases (n =190), 38 (15.%) patients returned after defaulting treatment, 50 (20.%) patients returned after failed treatment, 92 (37.7%) patients returned after relapse, 3 (1.2%) patients returned for treatment after being transferred to another health facility and 7 (2.%) patients returned for unspecified reasons. The median (range) age and weight of MDR-TB patients was 37 years (29-45.5) and 49.95 kg (43.7-54) respectively.

4.1.1.1 HIV - positive patients

Ninety-nine (40.%) HIV-positive patients with MDR-TB were involved in this study.

The 72.7% HIV-positive patients with available ART history were taking the following ARVs: stavudine (30 mg/po/bd), lamivudine (150 mg/po/bd) and efavirenz (600 mg/po/nocte).

4.1.1.2 HIV –negative patients

One hundred and forty-five (59.4%) HIV-negative patients with MDR-TB were included in the study.

4.1.2 Rifampicin mono-resistant TB patients

Of the 103 Rifampicin mono-resistant TB patients included in the study, 57 (55.3%) were males and 46 (44.%) were females. Fifty- two (50.%) were HIV–positive patients. Seventy- seven (74.%) patients had previously been treated with anti-TB drugs. Ninety-eight (95.%) patients were infected with pulmonary TB, and 4 (3.%) patients were infected with extrapulmonary TB. Twenty-six (25.2%) patients were new cases and 77 (74.%) were retreatment cases. Amongst the retreatment cases (n =77), 15 (14.%) patients returned after defaulting treatment, 18 (17.48%) patients returned after failed treatment, 39 (37.%) patients returned after relapse, 2 (1.9%) patients returned for treatment after being transferred to another health facility and 3 (2.9%) patients returned for unspecified reasons. The median (range) age and weight of Rifampicin mono-resistant TB patients was 38 years (31-45) and 50.5 kg (43-54.8) respectively.

4.1.2.1 HIV –positive patients

Fifty-two (50.%) HIV-positive patients with Rifampicin mono-resistant TB were included in the study. The 49 (94.2%) HIV-positive patients with available ART history were taking the following ARVs: stavudine (30 mg/po/bd), lamivudine (150 mg/po/bd), and efavirenz (600 mg/po/nocte).

4.1.2.2 HIV- negative patients

Fifty-one (49.5%) HIV-negative patients with Rifampicin mono-resistant TB were included in the study.

4.1.3 Isoniazid mono-resistant TB patients

Of the 39 (10.1%) Isoniazid mono-resistant TB patients included in the study, 19 (48.7%) were males and 20 (51.%) were females. Fourteen (35.9%) were HIV-positive patients. Twenty-six (66.%) patients had previously been treated with anti-TB drugs. Thirty-seven (94.%) patients were infected with pulmonary TB and 3 (5.1%) patients were infected with extrapulmonary TB.

Thirteen were new cases of Isoniazid mono-resistant TB and 26 (66.%) were retreatment cases. Amongst the retreatment cases (n =26), 7 (1%) patients returned after defaulting treatment, 5 (12.8%) patients returned after failed treatment and14 (35.9%) patients returned after relapse.
The median (range) age and weight of Isoniazid mono-resistant TB patients was 36 years (29-45) and 48.3 kg (40.5-52.5) respectively.

4.1.3.1 HIV – positive patients

Fourteen (35.9%) HIV-positive patients with Isoniazid mono-resistant TB were included in the study. The 14 (100%) HIV-positive patients with available ART history were taking the following ARVs: stavudine (30 mg/po/bd), lamivudine (150 mg/po/bd) and efavirenz (600 mg/po/nocte).

4.1.3.2 HIV- negative patients

Twenty- five (64.1%) HIV-negative patients with Isoniazid mono-resistant TB were included in the study.

Table 3:Description of the study population.

Patients' Characteristics	MDR-TB N= 244	Rifampicin mono-resistant TB N=103	Isoniazid mono-resistant TB N=39	Total N= 386
Sex				
Male	146 (59.8%)	57 (55.3%)	19 (48.7%)	222 (57.5%)
Female	98 (40.%)	46 (44.%)	20 (51.%)	164 (42.%)
Age				
<20 years	13 (5.3%)	2 (1.9%)	4 (10.%)	19 (4.9%)
21-30 years	59 (24.%)	23 (22.3%)	9 (23.%)	91 (23.%)
31-40 years	76 (31.%)	32 (31.%)	12 (30.77%)	120 (31.%)
41-50 years	65 (26.6%)	33 (32.0%)	11 (28.21%)	109 (28.2%)
>50 years	31 (12.7%)	13 (12.6%)	3 (7.%)	47 (12.%)
HIV status				
HIV-positive	99 (40.%)	52 (50.%)	14 (35.9%)	165 (42.%)
HIV-negative	145 (59.4%)	51 (49.5%)	25 (64.1%)	221 (57.%)
Antiretroviral therapy (of the patients with HIV)				
Total number	N=99	N=52	N=14	N=165
Yes	72 (72.7%)	49 (94.2%)	14 (100%)	135 (81.8%)
No	1 (1.0%)	2 (3.9%)		3 (1.8%)
Missing	26 (26.%)	1 (1.9%)		27 (16.%)
DR-TB history				
Never treated before	54 (22.1%)	26 (25.2%)	13 (33.3%)	93 (24.%)
Previously treated	190 (77.%)	77 (74.%)	26 (66.%)	293 (75.9%)
Patient's diagnostic category				
New cases	54 (22.1%)	26 (25.2%)	13 (33.3%)	93 (24.%)
Retreatment cases				
After default	38 (15.%)	15 (14.%)	7 (%)	60 (15.5%)
After transfer	3 (1.2%)	2 (1.9%)		5 (1.3%)

After relapse	92 (37.7%)	39 (37.%)	14 (35.9%)	145 (37.%)
After failure	50 (20.%)	18 (17.%)	5 (12.8%)	73 (18.9%)
Unknown	7 (2.%)	3 (2.9%)		10 (2.%)
DR-TB localization				
Pulmonary TB	227 (93.0%)	98 (95.%)	37 (94.%)	362 (98.%)
Extra-pulmonary TB	13 (5.3%)	4 (3.%)	2 (5.1%)	19 (49.2%)
Pulmonary and extra-pulmonary TB	4 (1.6%)	-	-	4 (1.0%)
Unknown	-	1 (1.0%)	-	1 (1.0%)

4.2: Immunological and virological profile in HIV-positive patients with drug resistant-TB

4.2.1 CD4 counts at baseline

The table below shows CD4 counts at baseline only. Table 36 and Table 37 show CD4 counts at 12 and 24 months respectively.

Table 4 shows a break-down per CD4 count of drug-resistant TB patients with available data involved in this study.

Table 4:Immunological profile in HIV-positive patients with drug resistant-TB

CD4 counts cells/mm^3 at baseline	**MDR-TB**	**RMR-TB**	**HMR-TB**
	N=99	N=52	N=14
< 200	24	23	1
200- 500	1	14	3
>500	6		1
Missing at baseline	51	52	7

From table 4, of the 48 HIV-positive patients with CD4 count results available at the time of the initiation of MDR-TB treatment, HIV-positive patients had a CD4 count of < 00 cells/mm^3. - HIV-positive patients had a CD4 count cells/mm^3-(Column 2/MDR-TB)

Of 43 HIV-positive patients with Rifampicin mono-resistant TB, with available CD4 count results at baseline of DR-TB treatment, had a CD4 count of < 00 cells/mm^3 had a CD4 count of 00 cells/mm^3.

Of 7 HIV-positive patients with Isoniazid mono-resistant TB, with available CD4 count results at baseline of DR-TB treatment, had a CD4 count of < 00 cells/mm^3 and had a CD4 count of cells/mm^3.

4.2.2: Virological profile

Among 13 MDR-TB patients with an available viral load data at baseline HIV-positive patients had a viral load of less than 40 copies/mL and 7 HIV-positive patients had a viral load ranging from 50 to 1,000,000 copies/mL. Only 1 HIV-positive patient had a viral load result at 12 months of MDR-TB treatment, with a viral load of 106-copies/ ml.

Out of 4 Rifampicin mono-resistant TB patients with an available viral load data at baseline- 2 HIV-positive patients had a viral load of less than 40 copies/mL and 2 HIV-positive patients had a viral load of 50-1,000,000 copies/mL.Isoniazid mono-resistant TB patients had no available viral load data.

4.3 Treatment outcomes

4.3.1. Treatment outcomes in drug-resistant TB patients

This section presents treatment outcomes of MDR-TB, RMR-TB, and HMR-TB patients.

Table 5:Treatment outcomes in drug-resistant TB patients

Outcomes	Cured	Failed	Unknown	Total

MDR-TB	104 (42.6%)	70 (30.7%)	65 (26.6%)	244
RMR-TB	42 (40.%)	21 (20.%)	40 (38.8%)	103
HMR-TB	22 (54.4%)	8 (20.5%)	9 (23.%)	39

4.3.2 MDR-TB patients

As shown in table 5, the cure rate for MDR-TB is 42.6%. The failure and unknown rate were 30.7% and 26.6% respectively. There were no differences in the treatment outcomes in MDR-TB patients.

4.3.3 Rifampicin mono- resistant TB patients

From the table above, the cure rate was 40.%. The failure rate was 20.%, and the unknown rate was 38.8%. There were no differences in the treatment outcomes in Rifampicin mono- resistant TB patients.

4.3.4 Isoniazid mono-resistant TB patients

There were no differences among the treatment outcomes in HMR-TB patients. The cure rate was 54.4%, failure rate was 20.5%, and unknown rate was 23.%.

4.4 Effect of age and sex on drug-resistant TB treatment outcomes

4.4.1 MDR-TB patients

Table 6: Effect of age and sex on MDR-TB treatment outcomes

Age group and sex	Cured	Failed	Unknown	Total

Age				
<20 years	9 (69.2%)	1 (7.%)	3 (23.%)	13 (5.3%)
21-30 years	26 (44.%)	18 (30.5%)	15 (25.4%)	59 (24.%)
31-40 years	32 (42.1%)	22 (2%)	22 (2%)	76 (31.%)
41-50 years	26 (40.0%)	23 (35.%)	16 (24.6%)	65 (26.6%)
>50 years	11 (35.%)	11 (35.%)	9 (29.0%)	31 (12.7%)
Total	104 (42.6%)	75 (30.7%)	65 (26.6%)	244 (100%)
Sex				
Male	61 (41.8%)	46 (31.5%)	39 (26.7%)	146 (59.8%)
Female	43 (43.%)	29 (29.%)	26 (26.5%)	98 (40.%)
Total	104 (42.6%)	75 (30.7%)	65 (26.6%)	244 (100%)

Table 6 shows the effect of age and sex on the treatment outcomes in MDR-TB patients. From the table above, the cure rate was 69.2%, 44.%, 42.1%, 40.0%, and 35.%, for patients in the agerange of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those older than 50 years of age respectively. The failure rate was 7.%, 30.5%, 28.9%, 35.%, and 35.% for patients in the agerange of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those older than 50 years of age respectively. The unknown rate was 23.%, 25.4%, 28.9%, 24.6% and 29.0% for patients in the age range 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those older than 50 years respectively. The differences among all these outcomes were not statistically significant.

As shown in the table above, the cure-rate was 41.% and 43.% in male and female patients respectively. The difference between the treatment outcomes in male and female MDR-TB patients is not statistically significant.

4.4.2 Rifampicin mono-resistant TB patients

Table 7:Effect of age and sex on the treatment outcomes in Rifampicin mono-resistant TB patients

Age group and sex	Cured	Failed	Unknown	Total
		Age		
<20 years	-	1 (50.0%)	1 (50.0%)	2 (1.9%)
21-30 years	9 (39.1%)	6 (26.%)	8 (34.8%)	23 (22.3%)
31-40 years	14 (43.%)	3 (9.%)	15 (46.%)	32 (31.%)
41-50 years	14 (42.4%)	6 (18.%)	13 (39.%)	33 (32.0%)
>50 years		5 (38.)	3 (23.%)	13 (12.6%)
Total	42 (40.%)	21 (20.%)	40 (38.8%)	103 (100%)
		Sex		
Male	22 (38.6%)	14 (24.%)	21 (36.8%)	57 (55.3%)
Female	20 (43.%)	7 (15.2%)	19 (41.3%)	46 (44.%)
Total	42 (40.%)	21 (20.%)	40 (38.8%)	103 (100%)

Table 7 shows the effect of age and sex on the treatment outcomes in Rifampicin mono-resistant –TB patients. The cure rate was 0%, 39.1%, 43.%, 42.4%, and 38.% for patients in the age range of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those above 50 years of age respectively.

The failure rate was 50.0%, 26.%, 9.%, 18.% and 38.% for patients in the age group of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those older than 50 years of age respectively. The unknown outcome rate was 50.0%, 34.%, 46.%, 39.%, and 23.% for patients in the agerange of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those older than 50 years of age respectively. The differences among all these outcomes were not statistically significant .

As shown in the table above, the cure rate was 38.6% and 43.% in male and female cases respectively. The differences between the treatment outcomes in male and female RMR-

TB patients were not statistically significant.

4.4.3. Isoniazid mono- resistant TB patients

Table 8: Effect of age and sex on the treatment outcomes in Isoniazid mono-resistant TB patients

Age group and sex	Cured	Failed	Unknown	Total
		Age		
<20 years	4 (100%)	-	-	4 (10.%)
21-30 years	3 (33.3%)	3 (33.3%)	3 (33.3%)	9 (23.%)
31-40 years	5 (41.7%)	2 (16.7%)	5 (41.7%)	12 (30.%)
41-50 years	8 (72.7%)	3 (27.%)	-	11 (28.2%)
>50 years	2 (66.7%)	-	1 (33.3%)	3 (7.%)
Total	22 (54.4%)	8 (20.5%)	9 (23.%)	39 (100%)
		Sex		
Male	11 (57.9%)	5 (26.3%)	3 (15.%)	19 (48.7%)
Female	11 (55.0%)	3 (15.0%)	6 (30.0%)	20 (51.%)
Total	22 (5.4%)	8 (20.5%)	9 (23.%)	39 (100%)

Table 8 shows the effect of age and sex on the treatment outcomes in Isoniazid mono-resistant TB patients. The cure rate was 100%, 33.3%, 41.7%, 72.7%, 66.7% for patients in the age range of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those above 50 years of age respectively. However, patients in the age range of 20 years and below, 41-50 years and those older than 50 years of age were more likely to be cured.

The failure rate was 0%, 33.3%, 16.7%, 27.%, and 0% for patients in the age range of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those above 50 years of age respectively. The unknown outcome rate was 0%, 33.3%, 41.7%, 33.3%, and 0% for

patients in the age range of 20 years and below, 21-30 years, 31-40 years, 41-50 years, and those older than 50 years of age respectively. The differences among all these outcomes were not statistically significant .

The cure rate was 57.% and 55.0% in male and female cases respectively. There were no significant differences in the treatment outcomes between male and female.

4.5: Effect of HIV-infection and antiretroviral therapy on drug-resistant TB treatment outcomes

4.5.1 MDR-TB patients

Table 9: Effect of HIV-infection and antiretroviral therapy on MDR-TB treatment outcomes

HIV status	Cured	Failed	Unknown	Total
Positive	42 (40.%)	37 (37.%)	20 (20.2%)	99 (40.%)
Negative	62 (59.6%)	38 (26.2%)	45 (31.0%)	145 (59.4%)
Total	104 (42.6%)	75 (30.7%)	65 (26.6%)	244 (100%)
Antiretroviral therapy (Efavirenz, stavudine, and lamivudine)				
Yes	30 (41.%)	28 (38.%)	14 (19.4%)	72 (72.7%)
No	-	-	1 (100%)	1 (1.00%)
Missing	12 (46.%)	9 (34.6%)	5 (19.2%)	26 (26.%)
Total	42 (42.4%)	37 (37.%)	20 (20.2%)	99 (100%)

Table 9 shows the effect of HIV status and antiretroviral therapy on the treatment outcomes in MDR-TB patients. The cure rate was 40.% and 59.6% in HIV-positive and HIV-negative patients infected with MDR-TB respectively. The failure rate was 37.3% and 26.2% in HIV-positive and HIV-negative patients respectively. The unknown rate was 20.2% and 31.0% in HIV-positive and HIV-negative patients respectively. The differences between all these outcomes were not statistically significant.

As shown in table 9, the cure rate was 41.% in HIV-positive patients with MDR-TB receiving antiretroviral therapy. The failed and unknown rate in HIV-positive patients receiving antiretroviral therapy was 38.% and 19.4% respectively. The cured, failed and unknown rate was 0%, 0% and 100% in HIV-positive patients not receiving ARVs, respectively. The cure rate was 46.% in HIV-positive patients with missing ARV data. The failure and unknown rate was 34.6%, and 19.2% in HIV-positive patients with missing ARV data respectively.

4.5.2 Rifampicin mono- resistant TB patients

Table 10: Effect of HIV-infection and antiretroviral therapy on RMR-TB treatment outcomes

HIV status	Cured	Failed	Unknown	Total
Positive	21 (40.38%)	8 (15.39%)	23 (44.23%)	52 (50.49%)
Negative	21 (41.18%)	13 (25.49%)	17 (33.33%)	51 (49.51%)
Total	42 (40.78%)	21 (20.39%)	40 (38.83%)	103 (100%)
Antiretroviral therapy (Efavirenz, Stavudine, and Lamivudine)				
Yes	20 (40.8%)	7 (14.%)	22 (44.9%)	49 (47.%)
No	1 (50.0%)	-	1 (50.00%)	2 (1.9%)
Missing		1 (100%)	-	1 (1.00%)
Total	21 (40.%)	8 (15.%)	23 (44.2%)	52 (50.%)

Table 10 shows the effect of HIV status and antiretroviral therapy on the treatment outcomes in Rifampicin mono-resistant TB patients. The cure rate was 40.38% and 41.18% in HIV-positive and HIV-negative patients with Rifampicin mono-resistant TB respectively. The failure rate was 15.%, and 25.% in HIV-positive and HIV-negative patients with Rifampicin mono-resistant TB respectively. Patients with unknown

outcomes accounted for 44.2%, and 33.3% in HIV-positive and HIV-negative respectively. The differences among all these outcomes were not statistically significant.

As shown in table 10, the cure rate was 40.82% and 50.00% in HIV-positive patients, with Rifampicin mono-resistant TB receiving antiretroviral therapy and HIV-positive patients with Rifampicin mono-resistant TB not receiving antiretroviral therapy respectively. No significant differences in the treatment outcomes were found between the two groups .

4.5.3 Isoniazid mono-resistant TB patients

Table 11: Effect of HIV-infection and antiretroviral therapy on HMR-TB treatment outcomes

HIV status	Cured	Failed	Unknown	Total
Positive	9 (64.%)	1 (7.1%)	4 (28.%)	14 (35.9%)
Negative	13 (52.0%)	7 (28.0%)	5 (20.0%)	25 (64.1%)
Total	22 (56.4%)	8 (20.51%)	9 (23.%)	39 (100%)
Antiretroviral therapy (Efavirenz, Stavudine, and Lamivudine)				
Yes	9 (64.%)	1 (7.1%)	4 (28.%)	14 (100%)
No	-	-	-	-
Missing	-	-	-	-
Total	9 (64.%)	1 (7.1%)	4 (28.)	14 (35.9%)

Table 11 shows the effect of HIV status and antiretroviral therapy on the treatment outcomes in Isoniazid mono-resistant TB patients. The cure rate was 64.% and 52.0% in HIV-positive and HIV-negative patients with HMR-TB respectively. The failure rate was 7.1%, and 28.0% in HIV-positive and HIV-negative patients with HMR-TB respectively. Patients with unknown outcomes were 28.%, and 20.0% in HIV-positive and HIV-

negative respectively. The differences between all these outcomes were not statistically significant.

As shown in table 11, the cure and failure rate was 64.29% and 7.1% respectively. The rate of unknown outcomes was 28.% in HIV-positive patients with Isoniazid mono-resistant TB receiving antiretroviral therapy respectively. No outcomes were recorded in HIV-positive patients with HMR-TB not receiving antiretroviral therapy due to insufficient data.

4.6 Influence of previous TB treatment on drug-resistant TB treatment outcomes

4.6.1 MDR-TB patients

Table 12: Influence of previous TB treatment on MDR-TB

Previous TB treatment	Cured	Failed	Unknown	Total
New	21 (38.%)	23 (42.%)	10 (18.5%)	54 (22.1%)
Previously treated with first-line drugs	25 (37.3%)	17 (25.%)	25 (37.3%)	67 (27.%)
Previously treated with second-line drugs	58 (47.16%)	35 (28.%)	30 (24.%)	123 (50.4%)
Total	104 (42.6%)	75 (30.7%)	65 (26.6%)	244 (100%)

As indicated in the table, the cure rate was 38.89%, 37.3% and 47.% in new patients, patients previously treated with first-line drugs and patients previously treated with second-line drugs, respectively. The failed and unknown rate was 42.%, 25.%, 28.% and 18.%, 37.3%, 24.% in new patients, patients previously treated with first-line drugs and patients previously treated with second-line drugs respectively. The differences among all these outcomes were not statistically significant.

4.6.2 Rifampicin mono- resistant TB patients

Table 13:Influence of previous TB treatment on rifampicin mono-resistant TB

Previous TB treatment	Cured	Failed	Unknown	Total
New	14 (53.%)	7 (26.9%)	5 (19.2%)	26 (25.2%)
Previously treated with anti-TB drugs	28 (36.%)	14 (18.%)	35 (45.%)	77 (61.5%)
Total	42 (40.%)	21 (20.%)	40 (38.8%)	103 (100%)

From the table above, the cure rate was 53.% and 36.% in new patients, and patients previously treated with anti-TB drugs respectively. The failure rate was 26.9% and 18.% in new patients, and patients previously treated with anti-TB drugs respectively. Patients with an unknown outcome rate were 19.2% and 45.% in new patients, and patients previously treated with anti-TB drugs respectively. There is a significant relationship between previous TB treatment and poor treatment outcomes in RMR-TB patients. Patients previously treated with anti-TB drugs were more likely to have poor treatment outcomes (P- value= 0.010).

4.6.3 Isoniazid mono-resistant TB patients

Table 14: Influence of previous TB treatment on Isoniazid mono-resistant TB

Previous TB treatment	Cured	Failed	Unknown	Total
New	7 (53.%)	4 (30.%)	2 (15.%)	13 (33.3%)
Previously treated with anti-TB drugs	15 (57.%)	4 (15.%)	7 (26.9%)	26 (66.%)

Total	22 (56.4%)	8 (20.5%)	9 (23.%)	39 (100%)

From the table above, the cure rate was 53.% and 57.% in new patients and patients previously treated with anti-TB drugs respectively. The failure rate was 30.% and 15.% in new patients and patients previously treated with anti-TB drugs respectively. The unknown outcome was 15.% and 26.9% in new patients and previously treated patients with anti-TB drugs respectively. The differences between all these outcomes were not statistically significant.

4.7 Influence of diagnostic categories on the treatment outcomes in drug-resistant TB patients.

4.7.1 MDR-TB patients

Table 15: on the treatment outcomes in MDR-TB patients

Patients diagnostic category	*Cured*	*Failed*	*Unknown*	*Total*
New cases	21 (39.6%)	23 (43.4%)	9 (1%)	54 (22.1%)
Retreatment cases				
After default	16 (42.1%)	11 (2%)	11 (2%)	38 (15.%)
After relapse	42 (45.%)	22 (23.9%)	28 (30.4%)	92 (37.%)
After failure	22 **(**44.0%)	14 (28.0%)	14 (28.0%)	50 (20.%)
After transfer	2 (66.%)	1 (33.3%)	-	3 (1.2%)
Other	1 (12.5%)	4 (50.0%)	3 (37.5%)	7 (2.%)
Total	104 (42.6%)	75 (30.7%)	65 (26.6%)	244 (100%)

Table 15 shows the influence of patients' diagnostic categor on the treatment outcomes in MDR-TB patients. The cure rate in new cases, after default, after relapse, after failure, after transfer and other cases was 39.6% 42.1%, 45.%, 44.0%, 66.%, and 12.5% respectively. The failure rate in new cases, after default, after relapse, after failure, after transfer and other cases was 43.4%, 28.9%, 23.9%, 28.0%, 33.3%, and 50.0%

respectively. The unknown rate in new cases, after default, after relapse, after failure, after transfer and other cases was 1%, 2%, 30.4%, 28.0% and 37.3% respectively. There is a significant P-value =0.001.

4.7.2 Rifampicin mono- resistant TB patients

Table 16: and treatment outcomes in Rifampicin mono-resistant TB patients

Patients diagnostic category	*Cured*	*Failed*	*Unknown*	*Total*
New cases	13 (50.0%)	8 (30.%)	5 (19.2%)	26 (25.2%)
		Retreatment cases		
After default	4 (26.%)	3 (20.0%)	8 (53.3%)	15 (14.%)
After relapse	14 (35.9%)	7 (1%)	18 (46.%)	39 (37.%)
After failure	10 (55.%)	2 (11.1%)	6 (33.3%)	18 (17.%)
After transfer	1 (100%)	-	-	1 (1.0%)
Total	42 (40.%)	21 (20.%)	40 (38.8%)	103 (100%)

Table 16 shows patients' diagnostic category according to the treatment outcomes in Rifampicin mono-resistant TB patients. The cure rates in new cases, after default, after relapse, after failure and after transfer cases were 50.0% 26.%, 35.9%, 55.%, and 100% respectively. The failure rates in new cases, after default, after relapse, and after failure cases, were 30.%, 20.0%, 1%, and 11.1% respectively. The unknown rates in new cases, after default, after relapse, and after failure cases were 19.2%, 53.3%, 46.%, and 33.3% respectively.

4.7.3 Isoniazid mono-resistant TB patients

Table 17: on the treatment outcomes in Isoniazid mono-resistant TB patients

Patients diagnostic category	Cured	Failed	Unknown	Total
New cases	7 (53.%)	4 (30.%)	2 (15.%)	13 (33.3%)
		Retreatment cases		
After default	5 (71.4%)	1 (14.%)	1 (14.%)	7 (1%)
After relapse	7 (50.0%)	2 (14.%)	5 (35.7%)	14 (35.9%)
After failure	3 (60.0%)	1 (20.0%)	1 (20.0%)	5 (12.8%)
After transfer				
Total	22 (56.4%)	8 (20.5%)	9 (23.%)	39 (100%)

Table 17 shows patients' diagnostic categor on the treatment outcomes in Isoniazid mono-resistant TB patients. The cure rates in new cases, after default, after relapse, after failure cases were 53.%, 71.4%, 50.0%, and 60.0% respectively. The failure rates in new cases, after default, after relapse, and after failure cases were 30.%, 14.%, 14.%, and 20.0% respectively. The unknown rates in new cases, after default, after relapse, and after failure cases was 15.%, 14.%, 35.7% and 20.0% respectively. The differences among all these outcomes were not statistically significant.

4.8 Effect of inappropriate (i.e. low or high) anti-TB drug dose on treatment outcomes

4.8.1 DR-TB patients

This section gives a breakdown of patients who received normal and inappropriate (low and high) dose of anti-TB drugs. It also gives a breakdown of normal and inappropriate (low and high) anti-TB drug dose, which patients were receiving per drug-resistant TB group.

The means procedure was used for comparative analysis of inappropriate (low) anti-TB drug dose on the treatment outcomes in the drug-resistant groups included in this study.

Table 18: Patients receiving inappropriate (i.e. low and high) and normal anti-TB drug dose in the study population

Anti-TB drugs	Number of patients receiving Low dose	Number of patients receiving high dose	Number of patients receiving normal dose	Total
Pyrazinamide	22 (13.%)	0	138 (86.%)	160
Kanamycin	7 (4.%)	1 (1.0%)	145 (94.%)	153
Ofloxacin	0	11 (12.2%)	79 (87.%)	90
Moxifloxacin	0	0	102 (100%)	102
Ethionamide	5 (3.1%)	12 (7.%)	144 (89.4%)	161
Ethambutol	6 (3.7%)	61 (37.%)	94 (58.%)	161
Terizidone	1 (1.0%)	0	145 (99.3%)	140
Isoniazid	1 (1.%)	41 (52.%)	36 (46.%)	78
Rifampicin	0	0	7 (100%)	7
Total	42	126	883	1051

As indicated in table 18, all DR-TB patients were included in the study with available drug dose data, with patients receiving 13.%, 4.%, 3.1%, 3.7%, 1.0% and 1.% of low dose Pyrazinamide, Kanamycin, Ehionamide, Ethambutol, Terizidone and Isoniazid respectively. Kanamycin, Ofloxacin, Ethionamide, Ethambutol, and Isoniazid were prescribed at a high dosage to 1.00%, 12.22%, 7.45%, 37.89%, and 52.56% of patients, respectively. Pyrazinamide, Kanamycin, Ofloxacin, Moxifloxacin, Ethionamide, Ethambutol, Terizidone, Isoniazid and Rifampicin were prescribed at normal dosages to 86.%, 94.%, 87.% 100%, 89.4%, 58.%, 99.3%, 46.%, and 100% of patients, respectively.

4.8.2. MDR-TB patients

Table 19: Number of patients receiving all normal anti-TB drug dose among MDR-TB patients

Total number of normal drug dose patients were receiving	Frequency of patients receiving normal anti-TB dose	Percentage of patients receiving normal anti-TB drug dose	Cumulative frequency of patients receiving normal anti-TB dose	Cumulative percentages of patients receiving normal anti-TB dose
0	120	49.	120	49.
1	11	4.5	131	53.
2	1	0.4	132	54.1
3	4	1.6	136	55.7
4	11	4.5	147	60.
5	46	18.	193	79.1
6	44	18.0	237	97.1
7	4	1.6	241	98.
8	3	1.2	244	100.

As indicated in the table above, 49.% of MDR-TB patients did not receive all normal anti-TB drug dose. The percentage of MDR-TB patients who received any 1, 2,3,4,5,6,7, and 8 normal anti-TB drug dose was 4.51%, 0.41%, and 1.64% 4.51%, 18.85%, 18.03%, and 1.64% respectively.

Table 20: Number of patients receiving any low anti-TB drug dose among MDR-TB patients

Total number of low drug dose patients were receiving	Frequency of patients receiving low anti-TB dose	Percentage of patients receiving low anti-TB drug dose	Cumulative frequency of patients receiving low anti-TB dose	Cumulative percentages of patients receiving low anti-TB dose
0	229	93.	229	98.

1	10	4.1	239	9
2	2	0.8	241	98.
3	2	0.8	243	99.
4	1	0.4	244	100

As shown in table 20, 93.% of MDR-TB patients did not receive any low anti-TB drug dose. The percentage of MDR-TB patients who received any one, two, three or four low anti-TB drug dose was 4.10%, 0.8%, 0.8% and 0.4% respectively.

Table 21: Number of patients receiving any high anti-TB drug dose among MDR-TB patients

Total number of high drug dose patients were receiving	Frequency of patients receiving high anti-TB dose	Percentage of patients receiving high anti-TB drug dose	Cumulative frequency of patients receiving high anti-TB dose	Cumulative percentages of patients receiving high anti-TB dose
0	180	73.	180	73.
1	60	24.	240	98.
2	2	0.8	242	99.
3	2	0.8	244	100

As shown in table 21, 73.% of MDR-TB patients did not receive any high anti-TB drug dose. The percentage of MDR-TB patients who received any 1,2, or 3 high anti-TB drug doses was 24.%, 0.8% and 0.8% respectively.

4.8.3 Rifampicin mono-resistant TB patients

Table 22: Number of patients receiving all normal anti-TB drug dose among Rifampicin mono-resistant TB patients

Total number of normal drug dose patients were receiving	Frequency of patients receiving normal anti-TB dose	Percentage of patients receiving normal anti-TB drug dose	Cumulative frequency of patients receiving normal anti-TB dose	Cumulative Percentages of patients receiving normal anti-TB dose
0	69	6	69	6
4	4	3.	73	70.
5	13	12.6	86	83.5
6	5	4.8	91	88.
7	11	10.	102	99.0
8	1		103	100

As shown in the table above, 6% of RMR-TB patients did not receive all normal anti-TB drug dosage. The percentage of RMR-TB patients who received any 4, 5, 6, 7 and 8 normal anti-TB drug dose was 3.%, 12.6%, 4%, 10.%, and % respectively.

Table 23: Number of patients receiving any low anti-TB drug dose among Rifampicin mono-resistant TB patients

Total number of low drug dose patients were receiving	Frequency of patients receiving low anti-TB dose	Percentage of patients receiving low anti-TB drug dose	Cumulative frequency of patients receiving low anti-TB dose	Cumulative percentages of patients receiving low anti-TB dose
0	87	84.	87	84.
1	14	13.	101	98.
2	2	1.9	103	100

As indicated in the table above, 84.% of RMR-TB patients did not receive any low anti-TB drug dose. The percentage of RMR-TB patients who received any 1 or 2 low anti-TB drug dose was 13.% and 1.9% respectively.

Table 24: Number of patients receiving any high anti-TB drug dose among Rifampicin mono-resistant TB patients

Total number of high drug dose patients were receiving	Frequency of patients receiving high anti-TB dose	Percentage of patients receiving high anti-TB drug dose	Cumulative frequency of patients receiving high anti-TB dose	Cumulative percentages of patients receiving high anti-TB dosage
0	73	70.87	73	70.87
1	26	25.24	99	96.12
2	4	3.88	103	100.00

As indicated in the table above, 70.% of RMR-TB patients did not receive any high anti-TB drug dose. The percentages of RMR-TB patients who received any 1or 2 high anti-TB drug dosewere 25.2%, and 3.% respectively.

4.8.4 Isoniazid mono- resistant TB patients

Table 25: Number of patients receiving any normal anti-TB drug dosage among Isoniazid mono-resistant TB patients

Total number of normal drug dose patients were receiving	Frequency of patients receiving normal anti-TB dose	Percentage of patients receiving normal anti-TB drug dose	Cumulative frequency of patients receiving normal anti-TB dose	Cumulative Percentages of patients receiving normal anti-TB dose

0	26	66.	26	66.
5	6	15.	32	82.
6	7		39	100

As indicated in the table above, 66. of HMR-TB patients did not receive all normal anti-TB drug dosage. The percentage of HMR-TB patients who received any 5 and 6 normal anti-TB drug dose was 15. and respectively.

Table 26: Number of patients receiving any high anti-TB drug dose among Isoniazid mono-resistant TB patients

Total number of high drug dose patients were receiving	Frequency of patients receiving high anti-TB dose	Percentage of patients receiving high anti-TB drug dose	Cumulative frequency of patients receiving high anti-TB dose	Cumulative percentages of patients receiving high anti-TB dose
0	20	51.	20	51.
1	16	41.0	36	92.3
2	3	7.	39	100

As indicated in the table above, 51. of HMR-TB patients did not receive any high anti-TB drug dose. The percentage of HMR-TB patients who received any 1 or 2 high anti-TB drug dose was 41.0% and 7.% respectively.

4.8.5 Effect of Inappropriate (low) anti-TB drug dose on the treatment outcomes in DR-TB patients

4.8.5.1 MDR-TB patients

Table 27: Effect of inappropriate (low) anti-TB drug dose on the treatment outcomes in MDR-TB patients

Outcomes	Patients who did not receive low anti-TB dose	Patients who received low anti-TB drug dose	Total
Cured	44 (37.6%)	3 (20.0%)	47
Failed	38 (32.%)	5 (33.3%)	43
Unknown	35 (29.9%)	7 (46.%)	42
Total	117	15	132

As indicated in table 27, the cure rate in MDR-TB patients who received low anti-TB drug dose and patients who did not receive low anti-TB drug dose was 20.00% and 37.6% respectively. The other outcome rates in patients who receive low anti-TB drug dose and patients who did not receive low anti-TB drug dose were 33.3% and 32.% failure, 46.% and 29.9% unknown respectively. The differences between all these outcomes were not statistically significant (p value= 0.3336).

4.8.5.2 Rifampicin mono- resistant TB patients

Table 28: The effect of inappropriate (low) anti-TB drug dose on the treatment outcomes in Rifampicin mono-resistant -TB patients

Outcomes	Patients who did not receive low anti-TB dose	Patients who received low anti-TB drug dose	Total
Cured	9 (33.3%)	6 (37.5%)	15
Failed	4 (14.8%)	6 (37.5%)	10
Unknown	14 (51.%)	4 (25.0%)	18

Total	27	16	43

As indicated in table 28, the cure rates in RMR-TB patients who received low anti-TB drug dose and RMR-TB patients who did not receive low anti-TB drug dose were 37.5% and 33.3% respectively. The other outcome rates in patients who received low anti-TB drug dose and patients who did not receive low anti-TB drug dose were 37.5% and 14.8% failure, 25.0% and 51.% unknown respectively.

Note: Isoniazid mono-resistant TB patients did not receive any low dose of anti- TB drugs.

4.9 Sputum culture conversion time

Tables 29, 30, and 31 show the sputum culture conversion time/rate in both HIV-positive and HIV-negative patients with MDR-TB, Rifampicin mono-resistant TB and Isoniazid mono-resistant TB respectively. The median time to sputum culture conversion by HIV-status was compared to the different drug-resistant group included in the study using the ICLIFETEST procedure (IC indicates interval censoring). The findings of this analysis are shown in figures 1,2 and 3 below. They also show the effects of normal, low and high anti-TB drug dose on the time to sputum culture conversion in MDR-TB, RMR-TB and HMR-TB patients respectively.

4.9.1 MDR-TB patients

Table 29: Sputum culture conversion time/ rate in HIV-positive and HIV-negative MDR-TB patients

Time sputum culture conversion	HIV-positive	HIV-negative	Total
	Number	Number	Number

occurred			
Within 60 days of treatment	60	88	148
Within 61-80 days	10	18	28
Within 81-100 days	8	15	23
Within 101-180 days	13	17	30
>180 days	2	3	5
Sputum cultures did not convert	6	4	10
Total	99	145	244

As indicated in table 29, of 244 MDR-TB patients, 229 (93.%) patients achieved sputum culture conversion within the intensive phase of MDR-TB treatment. These included 91 of 99 (91.9%) HIV-positive patients and 138 of 145 (95.%) HIV-negative patients. Overall, 96% (141 HIV-negative and 93 HIV-positive) patients from each study group obtained sputum culture conversion respectively. The sputum culture conversion rate was higher in the intensive phase (within 6 month) of treatment than in the continuation phase (within 7-24 months). The p-value shows that there are no significant differences in the time to sputum culture conversion between HIV positive and HIV-negative patients with MDR-TB (p= 0.98).

The median time to culture conversion was 36 days (IQR 24-72) and 40 days (IQR 26-72) in HIV-positive and HIV-negative MDR-TB patients respectively. There were no

significant differences in the time to sputum culture conversion by HIV- status in MDR-TB patients. As shown in Figure 1, the estimated survival probabilities are undetermined within the Turnbull intervals.

Figure 1: Nonparametric Survival Estimates comparing the time to sputum culture conversion by HIV status in MDR-TB patients

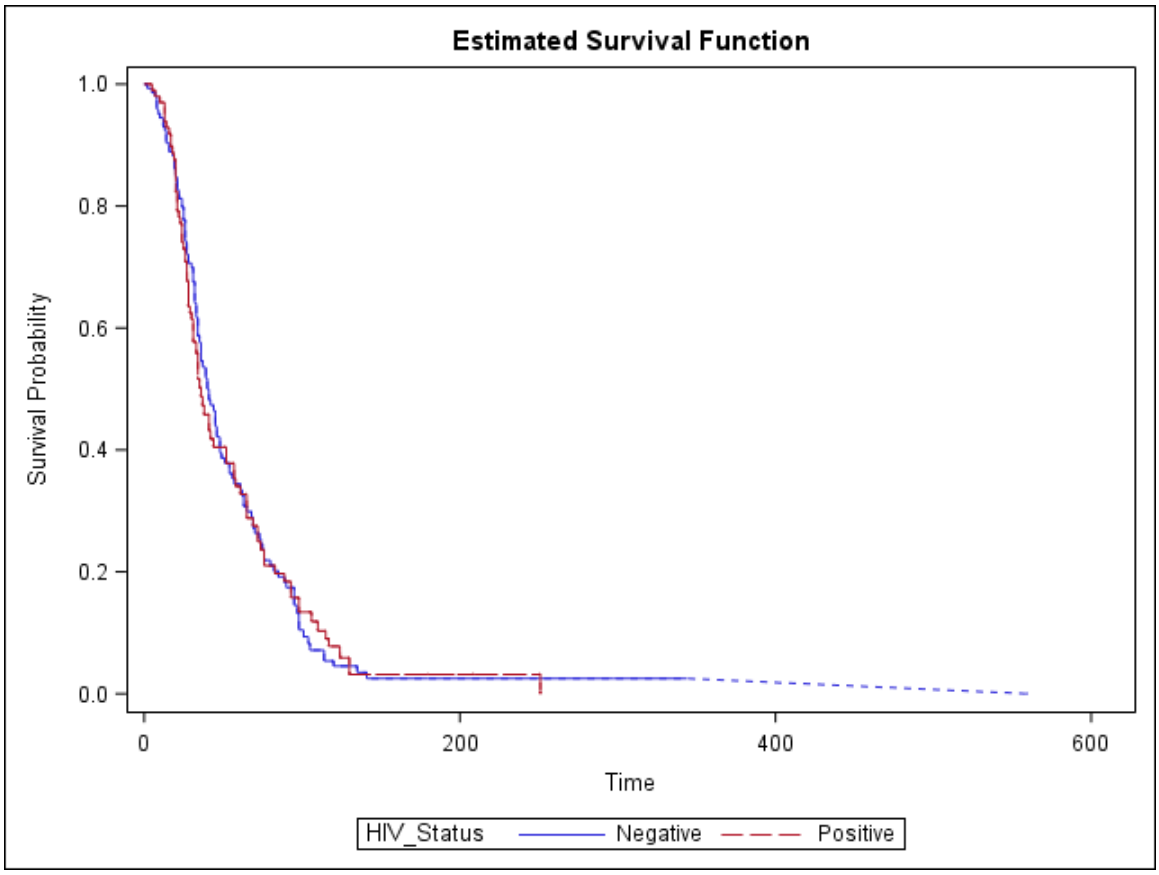


Figure 1 shows the survival probability amongst HIV-positive and HIV-negative patients with MDR-TB. The time from the date of initiation of TB treatment to the date of initial sputum culture conversion was defined in the methodology section. The time to sputum culture conversion by HIV status was compared using the ICLIFETEST procedure (IC indicates interval censoring). The ICLIFETEST procedure performs nonparametric survival analysis for interval-censored data. The first step in analyzing interval-censored data is to estimate the survival function. The survival function is a function of time that measures the probability that a subject will survive beyond a given time (SAS Institute

Inc, 2013). The estimated survival probabilities are undetermined within the Turnbull intervals, for ease of visualization; dashed lines are plotted across the Turnbull intervals for which the estimates are not defined (SAS Institute Inc, 2013).

4.9.2 Rifampicin mono- resistant TB patients

Table 30: Sputum culture conversion time/ rate in HIV-positive and HIV-negative Rifampicin mono-resistant TB patients

Time sputum culture conversion occurred	HIV-positive	HIV-negative	Total
	Number	Number	Number
Within 60 days of treatment	44	37	81
Within 61-80 days	6	7	13
Within 81-100 days	1	3	4
Within 101-180 days	0	4	4
>180 days	1	0	1
Sputum cultures did not convert	-	-	-
Total	52	51	103

As indicated in table 30 of the 52 HIV-positive and 51 HIV-negative Rifampicin mono-resistant TB patients with positive sputum culture results at the start of treatment, 102 (99.0%) achieved sputum culture conversion within the intensive phase of anti-TB treatment (first 6 months). These included 51 of 52 (98.%) HIV-positive patients and 51 of 51 (100%) HIV- negative patients. Overall, 100% (52 HIV-negative and 51 HIV-positive) patients from each study group obtained sputum culture conversion respectively. The sputum culture conversion rate was high, and almost all patients converted during the intensive phase (within 6 month) of treatment. The p-value shows that there are no significant differences in the time to sputum culture conversion between HIV positive and HIV-negative patients with Rifampicin mono-resistant TB (p= 0.14).

The median time to culture conversion was 26.5 days (IQR 16.5- 46) and 34 days (IQR 21-55) in HIV-positive and HIV-negative Rifampicin mono-resistant TB patients respectively There was no significant difference in the proportion of RMR-TB patients who converted by HIV status. As shown in Figure 2, the estimated survival probabilities are undetermined within the Turnbull intervals.

Figure 2: Nonparametric Survival Estimates comparing the time to sputum culture conversion by HIV status in RMR-TB patients

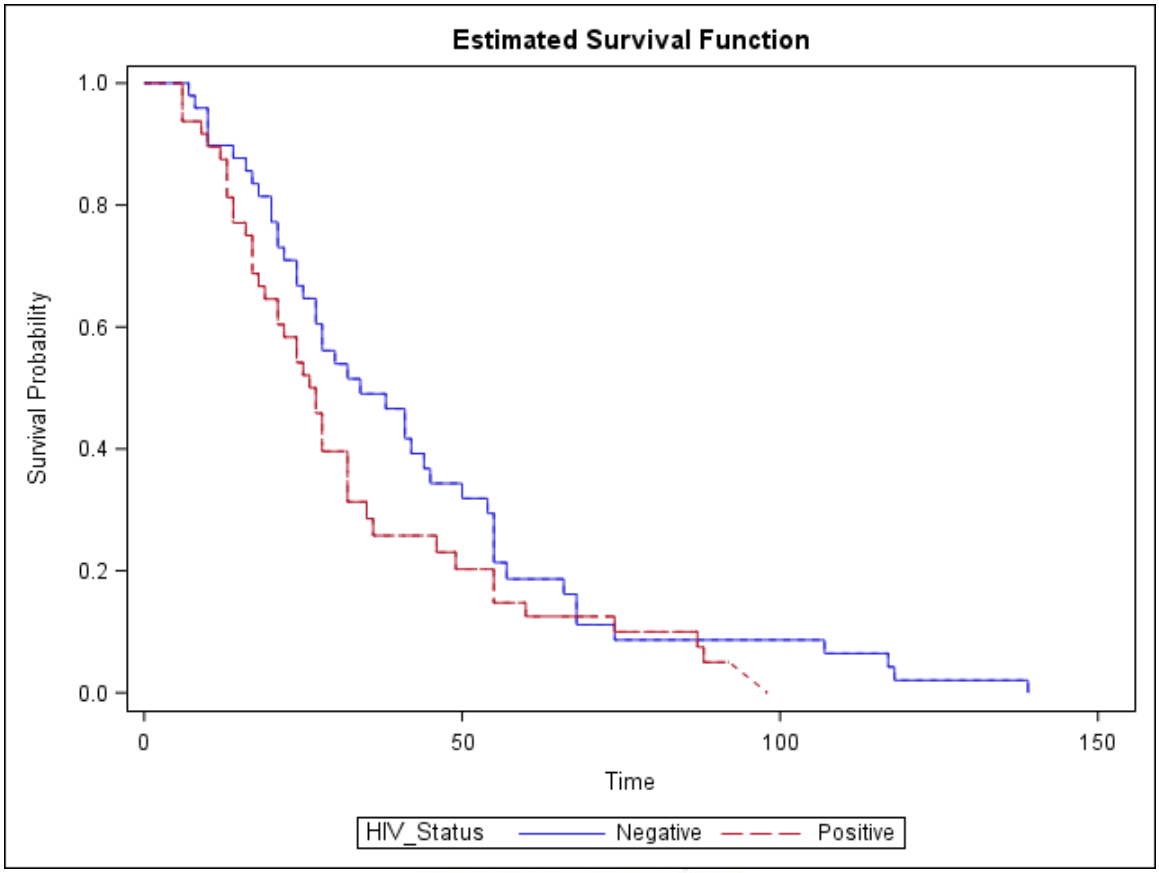


Figure 2 shows thesurviving amongst HIV-positive and HIV-negative patients with Rifampicin mono-resistant-TB. The time from the date of initiation of TB treatment to the date of initial sputum culture conversion was defined in the methodology section. The time to sputum culture conversion by HIV status was compared using the ICLIFETEST procedure (IC indicates interval censoring). The ICLIFETEST procedure performs nonparametric survival analysis for interval-censored data. The first step in analyzing interval-censored data is to estimate the survival function. The survival function is a function of time that measures the probability that a subject will survive beyond a given time (SAS Institute Inc, 2013). The estimated survival probabilities are undetermined within the Turnbull intervals, for ease of visualization; dashed lines are plotted across the Turnbull intervals for which the estimates are not defined (SAS Institute Inc, 2013).

4.9.3 Isoniazid mono- resistant TB patients

Table 31: Sputum culture conversion time/rate in HIV-positive and HIV-negative Isoniazid mono-resistant TB patients

Time sputum culture conversion occurred	HIV-positive	HIV-negative	Total
	Number	Number	Number
Within 60 days of treatment	5	8	13
Within 61-80 days	4	4	8
Within 81-100 days	-	3	3
Within 101-180 days	2	4	6
>180 days	3	5	8
Sputum cultures did not convert	-	1	1
Total	14	25	39

As indicated in table 31, of the 14 HIV-positive and 25 HIV-negative Isoniazid mono-resistant TB patients with positive sputum culture results at the start of treatment, 30 (76.9%) patients achieved sputum culture conversion within the intensive phase of anti-TB treatment (first 6 months). These included 11 of 14 (78.%) HIV-positive patients and 19 of 25 (76%) HIV-negative patients. Overall, 97.4% (24 HIV-negative and 14 HIV-positive) patients from each study group obtained sputum culture conversion respectively. The sputum culture conversion rate was higher in the intensive phase

(within 6 months) of treatment than in the continuation phase (within 7-24 months. The p-value shows that there are no significant differences in the time to sputum culture conversion between HIV-positive and HIV-negative patients with Isoniazid mono-resistant TB (p= 0.25).

The median time to culture conversion was 69 days (IQR 57-103) and 48 days (IQR 28-103) in HIV-positive and HIV-negative Isoniazid mono-resistant TB patients respectively. There was no significant difference in the time to sputum culture conversion by HIV status in HMR-TB patients. As shown in Figure 3, the estimated survival probabilities are undetermined within the Turnbull intervals.

Figure 3: Nonparametric Survival Estimates comparing the time to sputum culture conversion by HIV status in Isoniazid mono-resistant TB patients

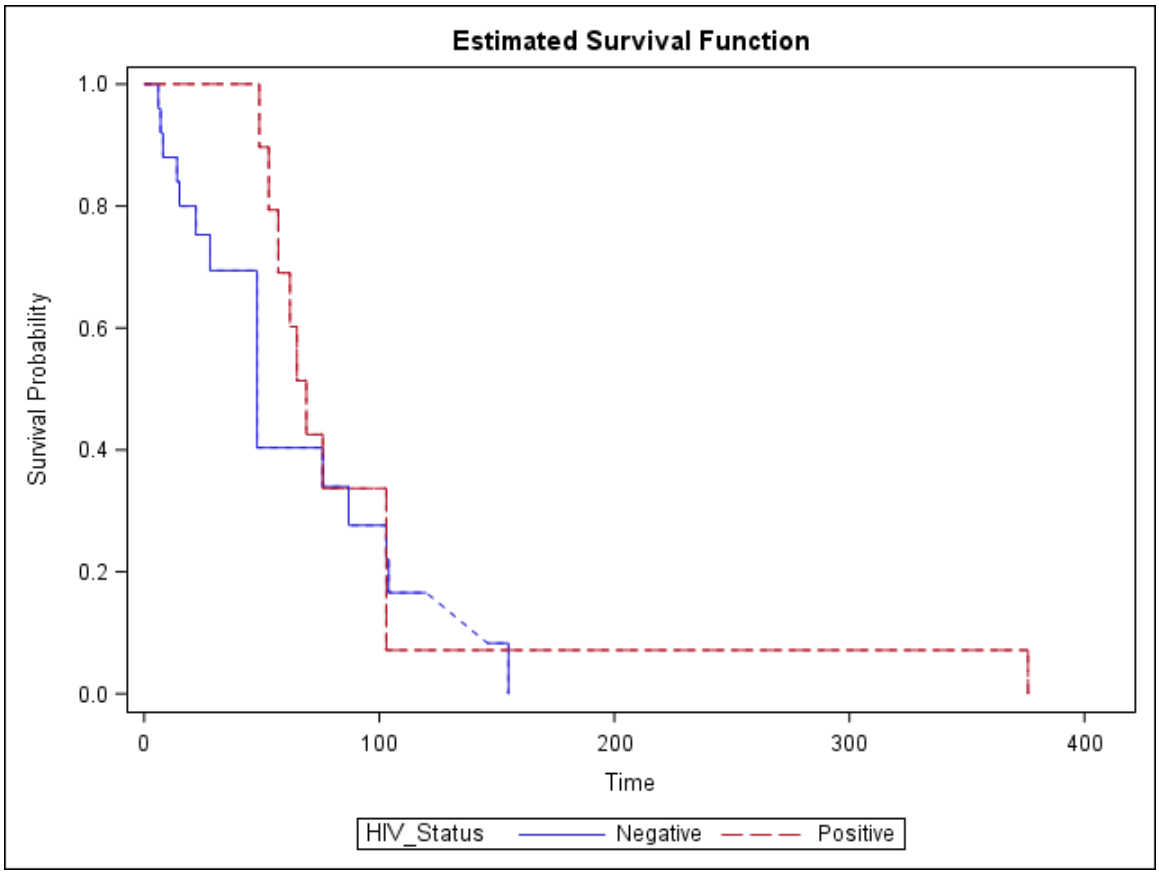


Figure 3 shows the surviving probabilityamongst HIV-positive and HIV-negative patients

with Isoniazid mono-resistant TB. The time from the date of initiation of TB treatment to the date of initial sputum culture conversion was defined in the methodology section. The time to sputum culture conversion by HIV status was compared using the ICLIFETEST procedure (IC indicates interval censoring). The ICLIFETEST procedure performs nonparametric survival analysis for interval-censored data. The first step in analyzing interval-censored data is to estimate the survival function. The survival function is a function of time that measures the probability that a subject will survive beyond a given time (SAS Institute Inc, 2013). The estimated survival probabilities are undetermined within the Turnbull intervals, for ease of visualization; dashed lines are plotted across the Turnbull intervals for which the estimates are not defined (SAS Institute Inc, 2013).

4.9.4. Effect of the dose of anti-TB drugs on the time to sputum culture conversion in MDR-TB patients

The effect of the dose of anti-TB drugs on the time to sputum culture conversion were analysed using the ICLIFETEST procedure (this was discussed in section 4.8). The ICLIFETEST procedure was used to get the estimates of the survival curves for each variable normal and inappropriate (low and high) anti-TB drug dose. Time to culture conversion in MDR-TB patients receiving inappropriate (low and high) anti-TB drug dose was compared to check the effect of inappropriate (low and high) anti-TB drug dose against the 'survival' time.

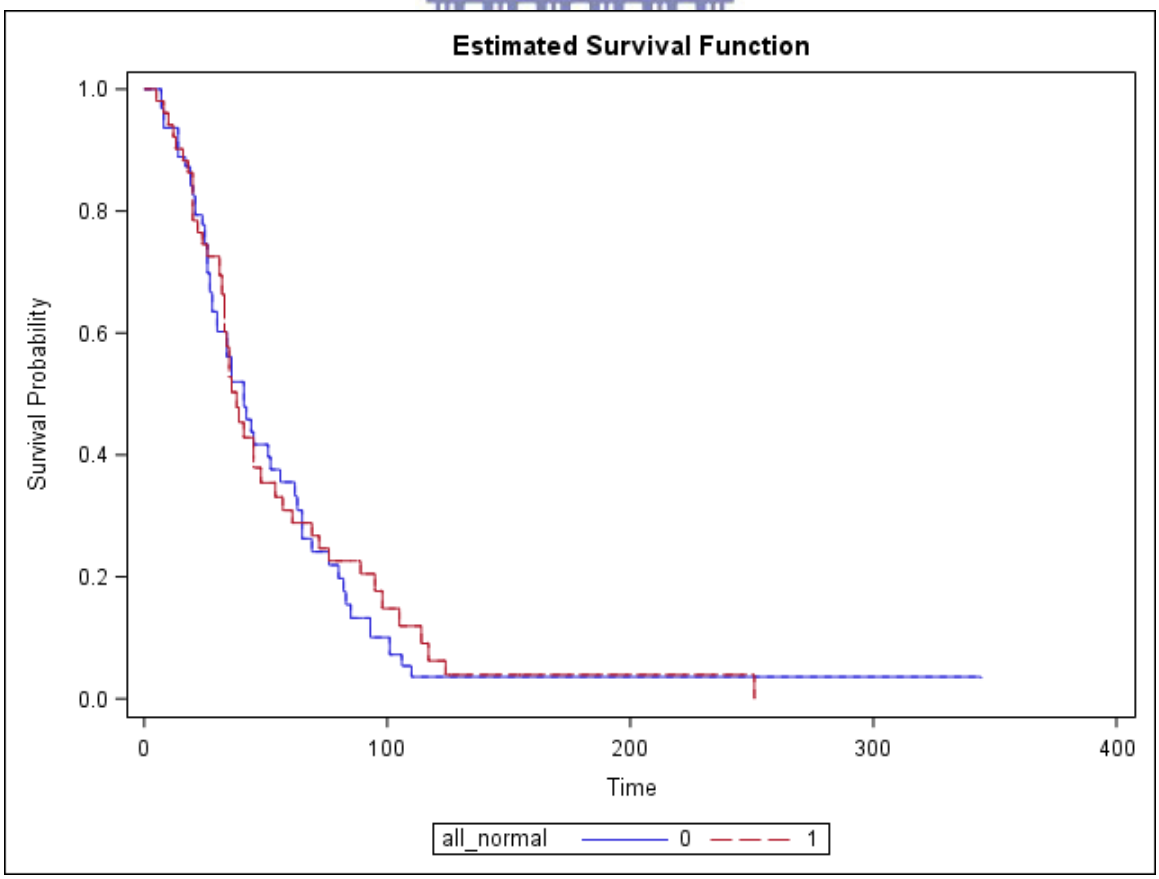
The median time to sputum culture conversion in MDR-TB patients who received all normal anti-TB drug dose and MDR-TB patients who did not receive all normal anti-TB drug dose was 38 days (IQR 24-72) and 41 days (IQR 25-69) respectively. There was no significant difference in the time to sputum culture conversion between patients who received all normal anti-TB drug dose and patients who did not receive all normal anti-TB drug dose (p- value was 0.66).

The median time to sputum culture conversion in MDR-TB patients who received any low anti-TB drug dosage and MDR-TB patients who did not receive any low anti-TB

drug dose was 35.5 days (IQR 21-101) and 38 days (IQR 25.5-69) respectively.No significant differences were observed between MDR-TB patients who received any low anti-TB drug dose and MDR-TB patients who did not receive any low anti-TB drug dose (p- value was 0.827).

The median time to sputum culture conversion in MDR-TB patients who received any high anti-TB drug dose and MDR-TB patients who did not receive any high anti-TB drug dose was 41 days (IQR 25-65) and 38 days (IQR 26-89) respectively.No significant difference was observed between MDR-TB patients who received any high anti-TB drug dose and MDR-TB patients who did not receive any high anti-TB drug dose (p- value was 0.34).

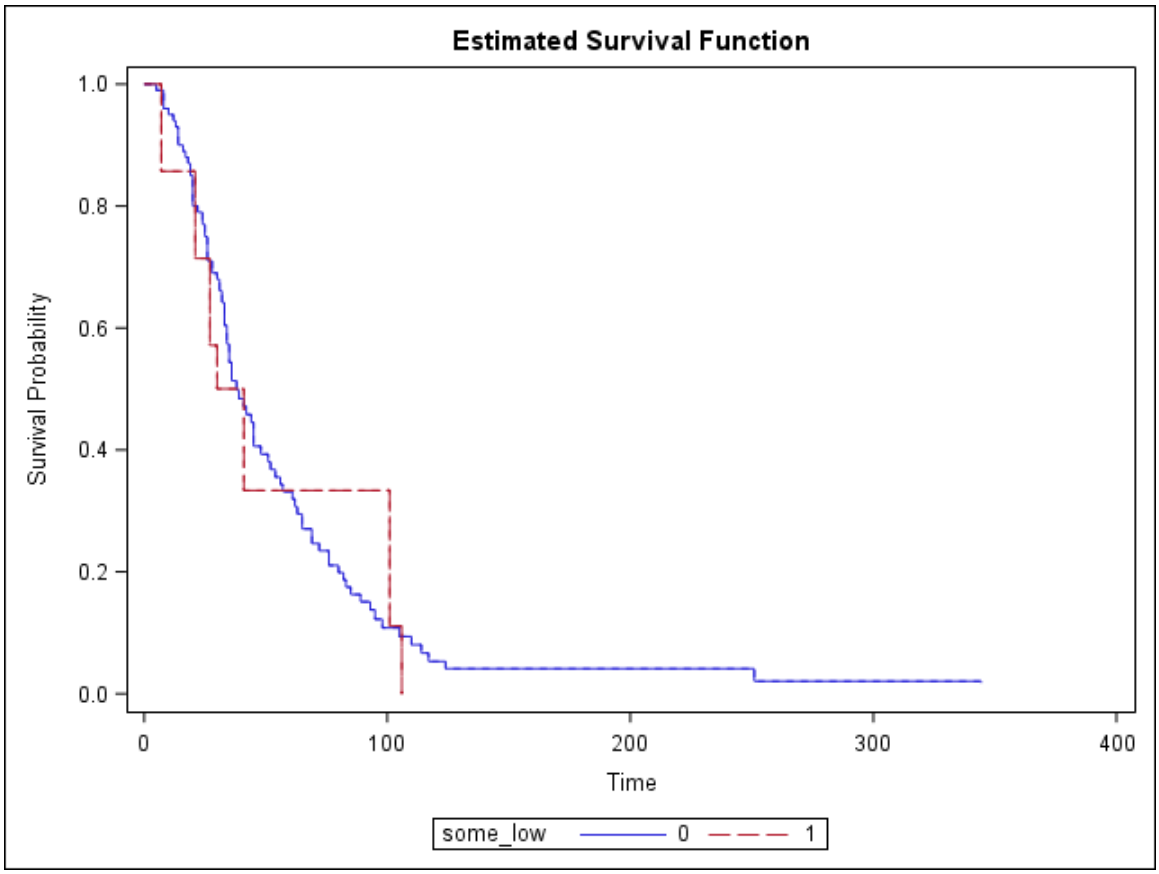
Figure 4: Nonparametric Survival Estimates comparing time to culture clearance by all normal anti-TB drug dose in MDR-TB patients



All normal=0 signifies patients who did not receive all normal anti-TB drug dose.
1= signifies patients who received all normal anti-TB drug dose.

Figure 4 shows the estimated survival. From the figure above, it can be seen that patients who received all normal anti-TB drug dose group of MDR-TB patients who did not receive all normal anti-TB drug dose. As shown in figure 4, the estimated survival probabilities are undetermined within the Turnbull intervals.

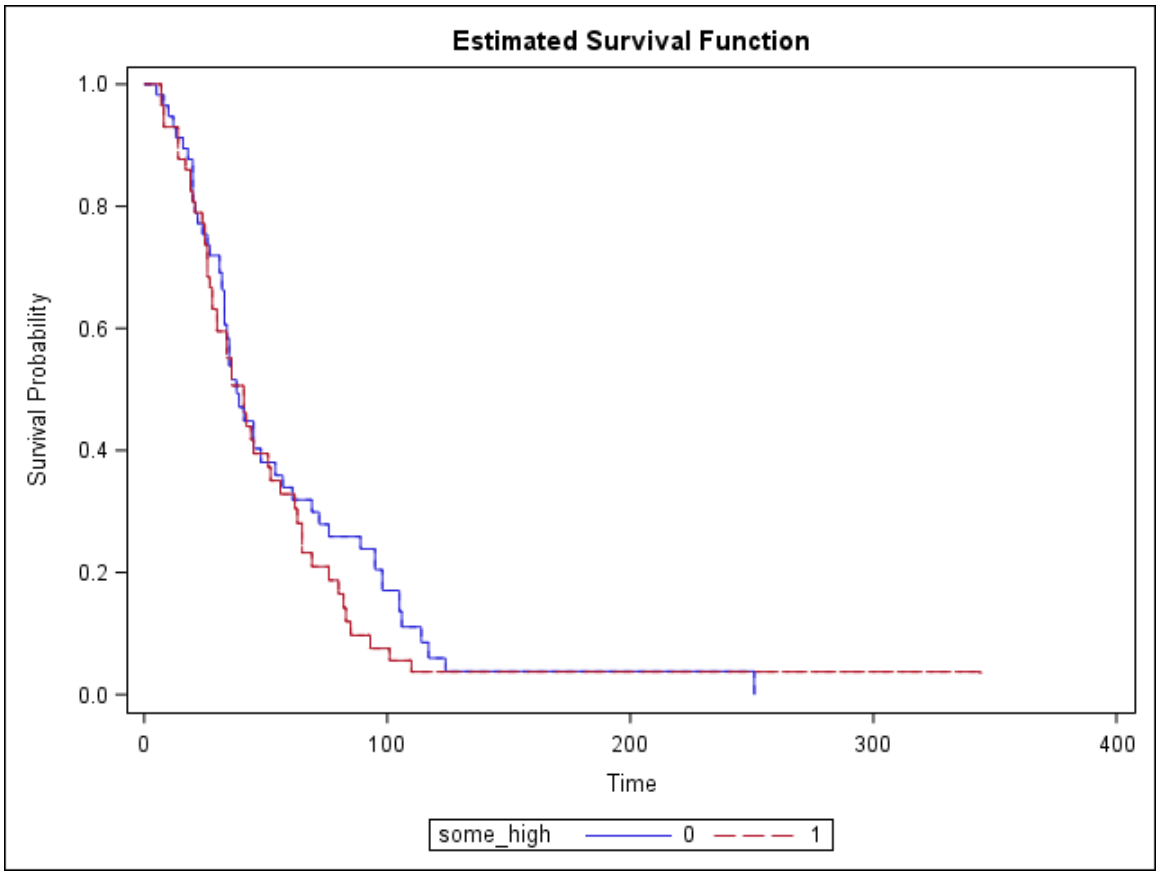
Figure 5: Nonparametric Survival Estimates comparing time to culture c by any low anti-TB drug dose in MDR-TB patients



Some low =0 signifies patients who did not receive any low anti-TB drug dose.
1= signifies patients who received any low anti-TB drug dose.

Figure 5 shows the estimated survival . Figure 5 shows clearly that patients who received any low anti-TB drug dose tend to have a lower survival rate before experiencing deterioration due to the effect of the low anti-TB drug dose than the group of MDR-TB patients who did not receive any low anti-TB drug dose. As shown in Figure 5, the estimated survival probabilities are undetermined within the Turnbull intervals.

Figure 6: Nonparametric Survival Estimates comparing time to culture c by any high anti-TB drug dose in MDR-TB patients



Some high=0 signifies patients who did not receive any high anti-TB drug dose.

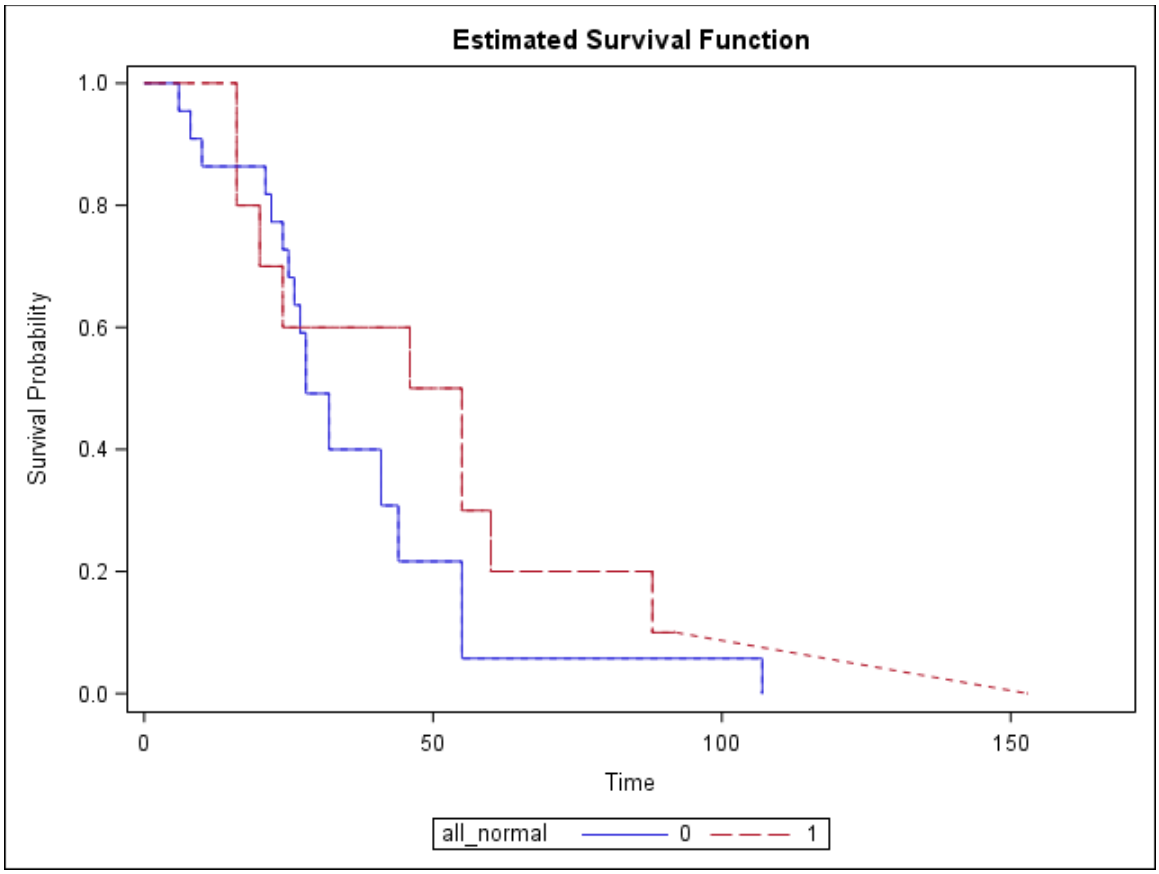
1= signifies patients who received any high anti-TB drug dose.

Figure 6 shows the estimated survival . From figure 6 it is revealed that patients who received any high anti-TB drug dose MDR-TB patients who did not receive any high anti-TB drug dose. Butclinical deterioration was faster in the group of MDR-TB patients

who did not receive any high anti-TB drug dose. As shown in Figure 6, the estimated survival probabilities are undetermined within the Turnbull intervals

4.9.5 Effect of the dose of anti-TB drugs on the time to sputum culture conversion in Rifampicin mono-resistant -TB

Figure 7: Nonparametric Survival Estimates comparing time to culture clearance by all normal anti-TB drug dose in Rifampicin mono-resistant-TB patients

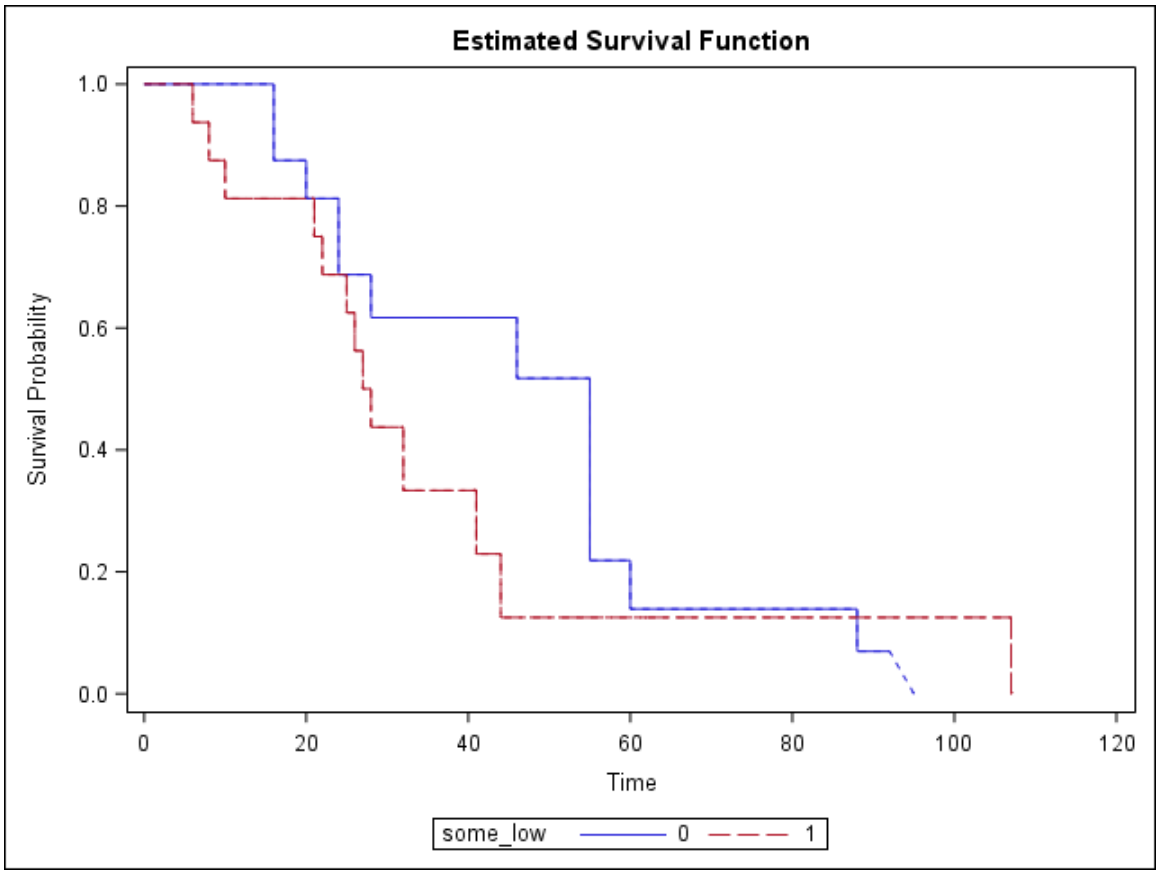


All normal=0 signifies patients who did not receive all normal anti-TB drug dose.
1= signifies patients who received all normal anti-TB drug dose.

Figure 7 shows the estimated survival . From figure 7 it was revealed that Rifampicin mono-resistant TB patients who received all normal anti-TB drug dose tend to survive

longer than RMR-TB patients who did not receive all normal anti-TB drug dose. As shown in figure 7, the estimated survival probabilities are undetermined within the Turnbull intervals.

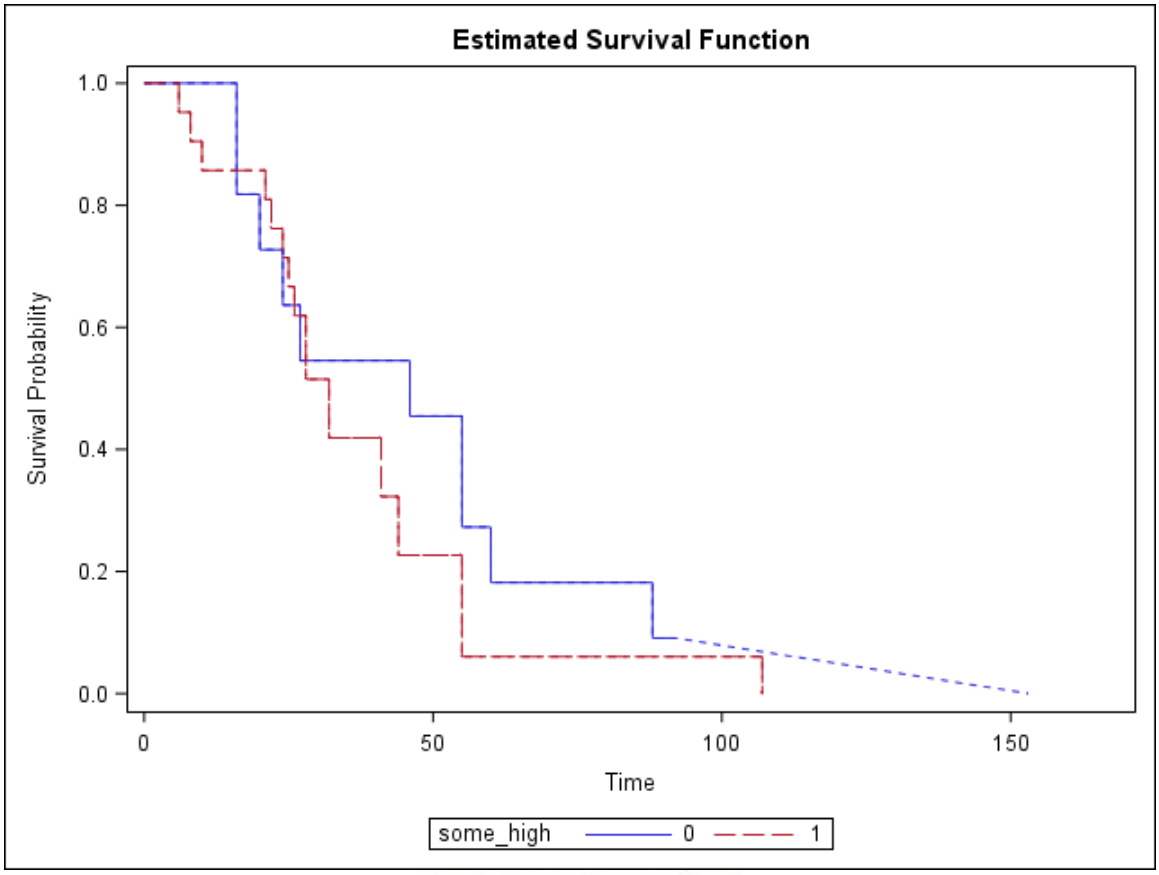
Figure 8: Nonparametric Survival Estimates comparing time to culture cby any low anti-TB drug dose in Rifampicin mono resistant-TB patients.



Some low =0 signifies patients who did not receive any low anti-TB drug dose.
1= signifies patients who received any low anti-TB drug dose.

Figure 8 shows the estimated survival . From figure 8 it was revealed that Rifampicin mono-resistant TB patients who received any low anti-TB drug dose RMR-TB patients who did not receive any low anti-TB drug dose. As shown in figure 8, the estimated survival probabilities are undetermined within the Turnbull intervals.

Figure 9: Nonparametric Survival Estimates comparing time to culture clearance by any high anti-TB drug dose in Rifampicin mono-resistant-TB patients.



Some high=0 signifies patients who did not receive any high anti-TB drug dose.

1= signifies patients who received any high anti-TB drug dose.

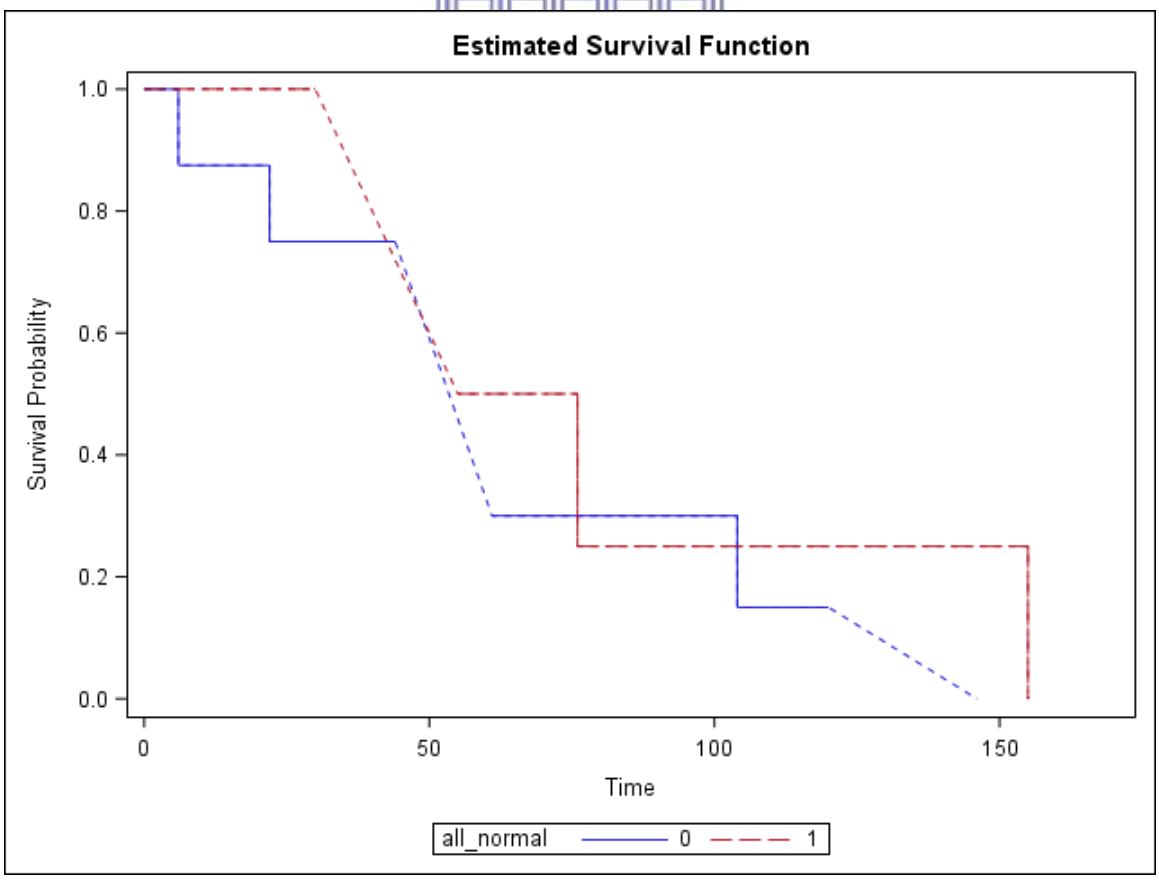
Figure 9 shows the estimated survival. From figure 9 it was revealed that RMR-TB patients who received any high anti-TB drug dose RMR-TB patients who did not receive any high anti-TB drug dose. As shown in figure 9, the estimated survival probabilities are undetermined within the Turnbull intervals.

4.9.6 Effect of anti-TB drug dose on the time to sputum culture conversion in Isoniazid mono-resistant TB patients

The median time to sputum culture conversion in Isoniazid mono-resistant TB patients who received all normal anti-TB drug dose and Isoniazid mono-resistant TB patients who did not receive all normal anti-TB drug dose was 76 days (IQR 55-155) and 61 days (IQR 61-104) respectively. No significant difference was observed in the time to sputum culture clearance between the 2 groups of patients (p- value was 0.036).

Note: Isoniazid mono-resistant TB patients did not receive any low anti-TB drug dose.
The median time to sputum culture conversion in Isoniazid mono-resistant TB patients who received any high anti-TB drug dose and Isoniazid mono-resistant TB patients who did not receive any high anti-TB drug dose was 61 days (IQR 61-104) and 55 days (IQR 76-155) respectively. No significant difference was observed in the time to sputum culture conversion between the 2 groups of patients (p- value was 0.33).

Figure 10: Nonparametric Survival Estimates comparing time to culture clearance by any normal anti-TB drug dose in Isoniazid mono resistant-TB patients

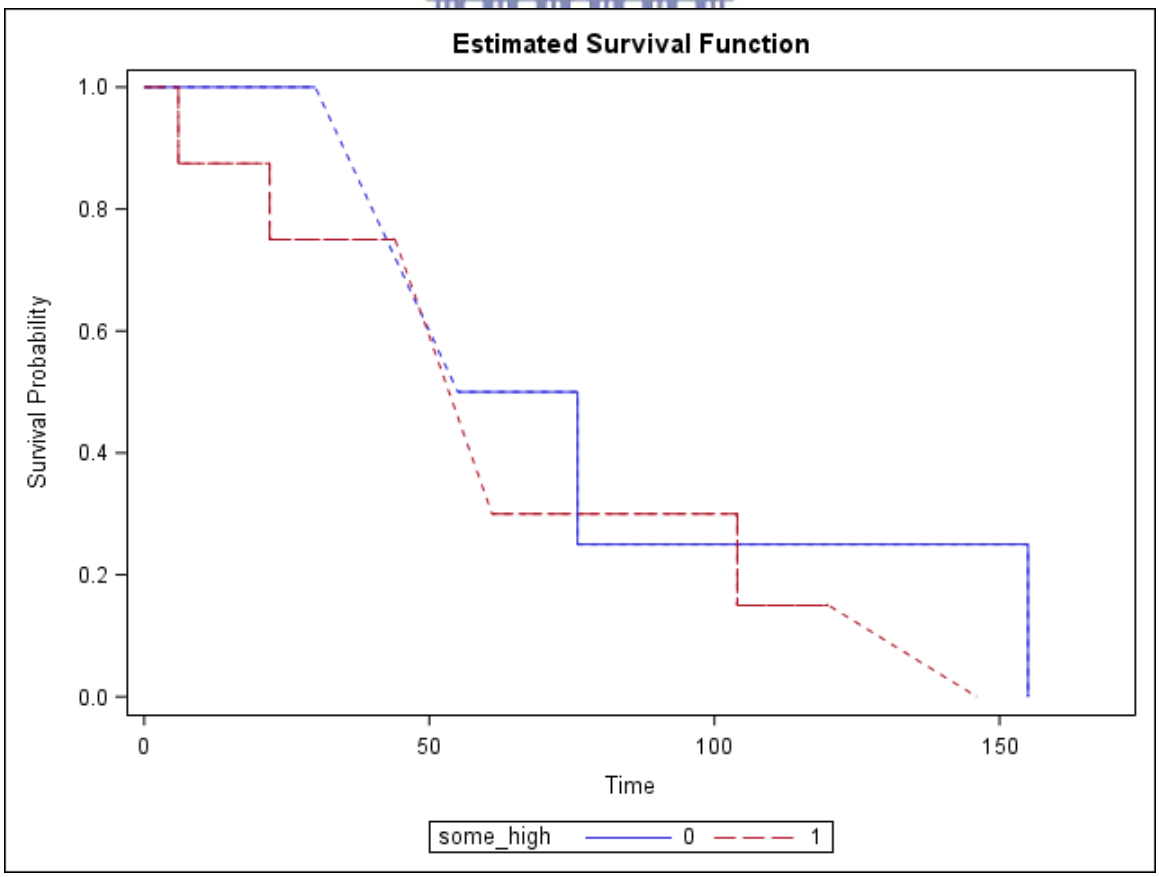


All normal=0 signifies patients who did not receive all normal anti-TB drug dose.
1= signifies patients who received all normal anti-TB drug dose.

Figure 10 shows the estimated survival . From figure 10 it was revealed that Isoniazid mono-resistant TB patients who received all normal anti-TB drug dose tend to survive longer before experiencing clinical deterioration than Isoniazid mono-resistant TB patients who did not receive all normal anti-TB drug dose. As shown in figure 10, the estimated survival probabilities are undetermined within the Turnbull intervals.

Isoniazid mono-resistant TB patients did not received any low anti-TB drug dose.

Figure 11: Nonparametric Survival Estimates comparing time to culture clearance by any high anti-TB drug dose in Isoniazid mono-resistant-TB patients



Some high=0 signifies patients who did not receive any high anti-TB drug dose.
1= signifies patients who received any high anti-TB drug dose.

Figure 11 shows the estimated survival . From figure 11 it was revealed that Isoniazid mono-resistant TB patients who received any high anti-TB drug dose Isoniazid mono-resistant TB patients who did not receive any high anti-TB drug dose

4.10 Influence of sputum culture conversion on treatment outcomes

The chi-square test was used to correlate the influence of sputum culture conversion time on the treatment outcomes in MDR-TB, RMR-TB and HMR-TB patients respectively.

4.10.1 MDR-TB patients

Table 32: Influence of sputum culture conversion on the treatment outcomes in HIV-positive and HIV-negative MDR-TB patients

Time to sputum culture conversion	Number of MDR-TB patients	Treatment outcomes, n (%) HIV-positive			Treatment outcomes, n (%) HIV-negative		
		Cured	Failed	Unknown	Cured	Failed	Unknown
Within 60 days of treatment	148 (60.%)	31(2%)	20 (13.5%)	9 (6.%)	42 (28.%)	19 (12.8%)	27 (18.2%)
Within 61-80 days	28 (11.%)	3 (10.7%)	4 (14.%)	3 (10.7%)	8 (28.%)	3 (10.7%)	7 (25.0%)
Within 81-100 days	23 (9.4%)	3 (16.%)	4 (22.2%)	1 (5.%)	7 (30.4%)	7 (30.4%)	1 (4.%)
Within 101-180 days	30 (12.3%)	4 (13.3%)	3 (10.0%)	6 (20.0%)	4 (13.3%)	6 (20.0%)	7 (23.3%)
>180 days	5 (2.5%)	1 (20.0%)	1 (20.0%)	-	1 (20.0%)	2 (40.0%)	-
Sputum cultures did not convert	10 (4.1%)	-	5 (50.0%)	1 (10.0%)	-	1 (10.0%)	3 (10.0%)
Total		42 (40.%)	37 (37.%)	20 (20.2%)	62 (59.6%)	38 (26.2%)	45 (31.0%)
	244	99			145		

Table 32 shows the sputum culture conversion rate and the treatment outcomes in MDR-TB patients by HIV status. The cure rate was 40.% and 59.6% in HIV-positive and HIV-negative patients with MDR-TB respectively. Of the 10 patients who never had sputum

culture conversion,6 failed the treatment and 4 had unknown outcomes. The failure rates in HIV-positive and HIV-negative patients were 37.% and 26.2% respectively. Patients with unknown outcomes were 20.2% and 31.0% respectively. The p- value was 0.030 in HIV-negative patients and 0.001 in HIV-positive patients. The p-value shows that treatment outcomes were statistically significantly worse for HIV-positive patients, despite early sputum culture conversion.

4.10.2. Rifampicin mono-resistant TB patients

Table 33: Influence of sputum culture conversion time on the treatment outcomes in HIV-positive and HIV-negative Rifampicin mono-resistant -TB patients

Time to sputum culture conversion	Number of RMR-TB patients	Treatment outcomes, n (%) HIV-positive			Treatment outcomes, n (%) HIV-negative		
		Cured	Failed	Unknown	Cured	Failed	Unknown
Within 60 days of treatment	81 (78.6%)	17 (2%)	7 (8.6%)	20 (24.%)	15 (18.5%)	10 (12.%)	12 (14.8%)
Within 61-80 days	13 (12.6%)	3 (23.%)	1(7.%)	2 (15.%)	1 (7.%)	2 (15.%)	4 (30.%)
Within 81-100 days	4 (3.%)	1 (25.0%)	-	-	2 (50.0%)	1 (25.0%)	-

Within 101-180 days	4 (3.%)	-	-	-	3 (75.0%)	-	1 (25.0%)
>180 days	1 (1.00%)	-	-	1 (100%)	-	-	-
Sputum cultures did not convert		-	-	-	-	-	-
Total		21 (40.%)	8 (15.%)	23 (44.2%)	21 (41.%)	13 (25.%)	17 (33.3%)
	103	52			51		

Table 33 shows the sputum culture conversion rate and the treatment outcomes in Rifampicin mono-resistant TB patients by HIV status. The cure rate was 40.% and 41.% in HIV-positive and HIV-negative patients with Rifampicin mono-resistant TB respectively. The failure rate in HIV-positive and HIV-negative patients was 15.% and 25.% respectively. The unknown outcome in HIV-positive and HIV-negative patients was 44.2% and 33.3% respectively. The p-value was 0.844 in HIV-negative patients and 0.922 in HIV-positive patients. The differences between all these outcomes were not statistically significant.

4.10.3 Isoniazid mono- resistant TB patients

Table 34: Influence of sputum culture conversion time on the treatment outcomes in HIV-positive and HIV-negative Isoniazid mono-resistant TB patients

Time to sputum culture conversion occurred	Number of HMR-TB patients	Treatment outcomes, n (%) HIV-positive			Treatment outcomes, n (%) HIV-negative		
		Cured	Failed	Unknown	Cured	Failed	Unknown
Within 60 days of treatment	13 (33.3%)	4 (30.%)	-	1 (7.%)	3 (23.%)	3 (23.%)	2 (15.%)
Within 61-80 days	8 (20.5%)	2 (25.0%)	1 (12.5%)	1 (12.5%)	3 (37.5%)	-	1(12.5%)
Within 81-100 days	3 (7.%)	-	-	1 (33.3%)	2 (66.%)	-	-
Within 101-180 days	6 (15.%)	3 (50.0%)	-	1 (33.3%)	2 (66.%)	-	-
>180 days	8 (20.5%)	-	-	-	3 (37.5%)	3 (37.5%)	2 (25.0%)
Sputum cultures did not convert	1 (2.%)	-	-	-	-	1 (100%)	-

Total		9 (64.%)	1 (7.1%)	4 (28.%)	13 (52.0%)	7 (28.0%)	5 (20%)
	39	14			25		

Table 34 shows the sputum culture conversion time/rate and the treatment outcomes in Isoniazid mono-resistant TB patients by HIV status. The cure rate was 64.% and 52.0% in HIV-positive and HIV-negative patients with Isoniazid mono-resistant TB respectively. The failure rates were 7.1% and 28.0% respectively. The unknown outcome was 28.% and 20.0% respectively. Only 1 patient did not achieve sputum culture conversion, and he failed the treatment. The P-value was 0.013 in HIV-negative patients and 0.159 in HIV-positive patients.

4.11 Sputum culture reversion

We noticed that DR-TB patients could achieve sputum culture conversion at the intensive phase of treatment and become culture-positive again during the continuation phase of treatment.

4.11.1 MDR-TB patients

Of the 229 (93.%) MDR-TB patients who achieved initial sputum culture conversion within the intensive phase of treatment as shown in table 20, 14 (6.1%) MDR-TB patients' sputum culture reverted during the continuation phase of treatment. This includes 3 HIV-positive and 11 HIV-negative patients with MDR-TB. The treatment outcomes of these patients were: 11 failed, and 3 patients had unknown outcomes (Table not included).

4.11.2 RMR-TB patients

Out of 102 (99.0%) RMR-TB patients who achieved initial sputum culture conversion within the intensive phase of treatment as shown in table 21, 2 (%) RMR-TB patients' sputum culture reverted during the continuation phase of treatment. This includes 1HIV-positive and 1HIV-negative patients. The treatment outcomes of the 2 patients were: 1 failed, and 1 had unknown outcomes (table not included).

4.11.3. HMR-TB patients

There was no reversion after initial culture conversion in all 39 Isoniazid mono-resistant TB patients.

4.11.4 TB localization and sputum reconversion in HIV–positive patients

Table 35: TB localization and sputum culture reconversion in HIV-positive patients with MDR-TB and Rifampicin mono-resistant -TB

TB localization	MDR-TB patients			RMR-TB patients		
	HIV - positive	Conversion within 6 months	Reversion after initial conversion	HIV - positive	Conversion within 6 months	Reversion after initial conversion
Pulmonary TB	91	84 (92.3%)	3 (3.57%)	50	49 (98.0%)	1 (2.04%)
Extrapulmonary TB	7	6 (85.7%)	-	1	1 (100%)	-
Pulmonary TB and extrapulmonary TB	1	1 (100%)	-	1	1 (100%)	-
Total	99	91	3	52	51	1

Table 35 shows TB localization and sputum culture reversion in HIV-positive patients with MDR-TB and RMR-TB. It shows that only 3 (3.%) and 1 (2.0%) of pulmonary TB patients with HIV infection reverted during the continuation phase of MDR-TB and RMR-TB treatment.

Isoniazid mono-resistant TB patients did not revert sputum culture after initial sputum culture conversion.

4.12 Influence of the immunological and virological profile on the treatment outcomes in drug resistant-TB patients

The CD4 count, viral load parameters and treatment outcomes in HIV-positive patients with MDR-TB, RMR-TB and HMR-TB are compared using the Kruskal-Wallis test to see if there are any differences among the CD4 count, with viral load parameter at different intervals on the treatment outcomes. The Kruskal-Wallis one way analysis of variance is a non-parametric method and its equivalent is the one-way analysis of variance (ANOVA). Due to the skewness of the data, the Kruskal-Wallis test was used to correlate the influence of CD4 count cells and viral load values to check for significant differences in the treatment outcomes of HIV-positive patients with DR-TB.

4.12.1 MDR-TB patients

4.12.1.1. CD4 counts

In table 36 of the 48 HIV-positive patients with CD4 count results available at the time of MDR-TB treatment initiation (Table 5), only 22 patients were cured with a median CD4 count of 230 (IQR 75-465) cells/mm^3, 17 patients failed treatment and 19 patients had unknown outcomes. Of the 48 patients with CD4 data at baseline only, 10 HIV-positive MDR-TB patients had a CD4 count data available at the end of twelve months of treatment. Of these 10 patients, only 4 were cured, 5 failed and 1 had unknown outcomes. Of these 10 HIV-positive patients with available data at 12 months of treatment, 6 patients had a decreased CD4 count when compared to baseline and 4 patients had an increased CD4 count when compared to baseline. The median CD4 count of the 4 patients who were cured was 258 (IQR 166-377.50) cells/mm^3.

Among 48 HIV–positive patients with CD4 counts data at baseline only 5 HIV-positive patients had CD4 count data available at the end of 24 months of MDR-TB treatment. Of these 5 patients only 3 were cured, with a CD4 count of 311 (IQR 225-515) cells/mm^3 and 2 failed treatment. Of these 5 HIV-positive patients with CD4 counts at 24 months of treatment, 3 patients had a decreased CD4 count when compared to baseline and 2 patients had an increase in CD4 count when compared to baseline.

4.12.1.2 Viral load

Among MDR-TB patients with HIV viral load test result at baseline (n= 12), only 4 patients were cured with a median of 40 (IQR 40 -1507.50) VL, 5 patients failed treatment and the outcomes of the other 3 patients was unknown. Of the 12 MDR-TB patients only 1 patient had an available HIV viral load at the end of 12 months of treatment. This patient failed treatment and had a decrease in viral load when compared to baseline. As indicated in table 36, there are no significant differences in the CD4 count cells and viral load at baseline, baseline and 12 months and baseline and 24 months on the treatment outcomes in HIV-positive patients with MDR-TB. There were insufficient data to compare viral load at baseline and viral load at 12 months. he p value 0.03. The

4.12.2 RMR-TB patients

4.12.2.1 CD4 counts

In table 37, of the 43 HIV-positive RMR-TB patients with CD4 count results available at the time of DR-TB treatment initiation (Table 5), only 17 patients were cured with a median CD4 count of 308 (IQR 111-338) cells/mm^3, 6 patients failed and 20 patients' outcomes were unknown. Of the 43 HIV–positive patients with RMR-TB only 4 HIV-positive patients had a CD4 count available at the end of twelve months of treatment. Of these 4 patients, 2 were cured and 2 failed treatment. The median CD4 count of the 2 patients cured was 117 (IQR 35-199) cells/mm^3. Of these 4 patients, 2 patients had a decrease in CD4 count when compared with baseline and the other 2 patients had an increase in CD4 count when compared with baseline. Among the 43 HIV–positive RMR-TB patients, only 2 HIV-positive patients had a CD4 count data available at the end of 24 months of DR-TB treatment. Of these 2 patients 1 was cured, with a CD4 count of 515 (IQR 515-515) cells/mm^3, and the other patient's treatment outcome was unknown. Of these 2 patients, 1 patient had a decrease in CD4 count when compared with baseline and the other patient had an increase in CD4 count when compared with baseline.

4.12.2.2. Viral load

Among Rifampicin mono-resistant-TB patients with HIV viral load test result at baseline (n= 4), only 2 patients were cured with a median of 58 (IQR 40 -76) VL and the outcome of the other 2 patients was unknown. There were no data to compare the viral load at the end of 12 months in the RMR-TB patients**.**

As indicated in Table 37, 0.683

4.12.3. HMR-TB patients

Of the 7 HIV-positive patients with Isoniazid mono-resistant TB with CD4 count results available at the time of DR-TB treatment initiation (Table 5), 6 patients were cured with a median CD4 count of 208 (IQR 123-313) cells/mm^3 and one patient's outcome was unknown. There were insufficient CD4 and viral load data to compare the CD4 and viral load in this group of patients. he p-value was 0.13 in HMR-TB-positive patients.

Table 36: The effect of immunological and virological profile on the treatment outcomes at different intervals in HIV- positive MDR-TB patients.

Outcomes	N	Variables	N	25th percentile	Median	75th percentile	Minimum	Maximum
Cured	**42**	CD4 count at baseline	22	75.00	230.00	465.00	4.00	811.00
		CD4 count at 12 months	4	166.00	258.00	377.50	133.00	438.00
		CD4 count at 24 months	3	225.00	311.00	515.00	225.00	515.00
		Viral load at baseline	4	40.00	40.00	1507.50	40.00	3055.00
		Viral load at 12 months	-					
Failed	**37**	CD4 count at baseline	17	119.00	207.00	279.00	34.00	564.00
		CD4 count at 12 months	5	64.00	135.00	188.00	42.00	748.00
		CD4 count at 24 months	2	65.00	111.00	157.00	65.00	157.00
		Viral load at baseline	5	421.00	1438.00	3300.00	256.00	8414.00
		Viral load at 12 months	1	106.00	106.00	106.00	106.00	106.00
Unknown	**20**	CD4 count at baseline	9	53.00	126.00	207.00	18.00	414.00
		CD4 count at 12 months	1	36.00	36.00	36.00	36.00	36.00
		CD4 count at 24 months	1	178.00	178.00	178.00	178.00	178.00

Viral load at baseline	3	40.00	40.00	183.00	40.00	183.00
Viral load at 12 months	-	-	-	-	-	-

Table 37: The effect of immunological and virological profile on the treatment outcomes at different intervals in HIV- positive Rifampicin mono-resistant TB patients

Outcomes	N	Variables	N	25th percentile	Median	75th percentile	Minimum	Maximum
Cured	**21**	CD4 count at baseline	17	111.00	308.00	338.00	15.00	754.00
		CD4 count at 12 months	2	35.00	117.00	199.00	35.00	199.00
		CD4 count at 24 months	1	515.00	515.00	515.00	515.00	515.00
		Viral load at baseline	2	40.00	58.00	76.00	40.00	76.00
		Viral load at 12 months	-	-	-	-	-	-
Failed	**8**	CD4 count at baseline	6	7.00	107.50	207.00	2.00	575.00
		CD4 count at 12 months	2	190.00	205.50	221.00	190.00	221.00
		CD4 count at 24 months	-	-	-	-	-	-
		Viral load at baseline	-	-	-	-	-	-
		Viral load at 12 months	-	-	-	-	-	-
Unknown	**23**	CD4 count at baseline	20	39.50	110.50	303.00	4.00	1068.00
		CD4 count at 12 months	-	36.00	36.00	36.00	36.00	36.00
		CD4 count at 24 months	1	156.00	156.00	156.00	156.00	156.00

Viral load at baseline	2	40.00	167156.00	334272.00	40.00	334272.00
Viral load at 12 months	-	-	-	-	-	-

4.13. Influence of the duration (days) of antiretroviral therapy on TB treatment outcomes in HIV-positive patients with MDR-TB

The duration of ART was measured from the start of ARV therapy until the time anti-TB treatment was initiated. The data shown in the tables below were collected from the folders of HIV-positive patients who were on ART before MDR-TB treatment was initiated. Due to the skewness of the ART duration data, the Kruskal-Wallis one way analysis of variance was used to correlate the duration of antiretroviral therapy on the treatment outcomes in MDR-TB patients.

Table 38: Influence of the duration (days) of antiretroviral therapy on MDR-TB treatment outcomes in HIV-positive patients

Treatment Outcomes	Number observed	Number missing	25th percentile	Median	75th percentile	Minimum	Maximum
Cured	13	29	29.0000	82.0000	727.0000	19.0000	1630.0000
Failed	8	29	136.0000	273.0000	643.5000	18.0000	1897.0000
Unknown	4	16	276.5000	736.0000	1398.0000	48.0000	1829.0000

Numbersreported in table 38 indicate number of HIV-positive patients with ART duration. Number missing indicates HIV-positive patients with missing data on ART duration. 25thpercentile indicates the lower interquartile range of ART duration in HIV-positive patients. Medianindicates middle interquartile range of ART duration in HIV-patients. 75th percentile indicates upper interquartile range of ART duration in HIV-positive patients. Minimum indicates the least ART duration period in days. Maximum indicates the highest ART duration period in days.

Table 38 shows the influence of duration of antiretroviral therapy on MDR-TB treatment outcomes in HIV-positive patients. From the table above, the median duration of antiretroviral therapy in HIV-positive patients who were cured was 82 days (IQR 29-727). The median duration of antiretroviral therapy in HIV-positive patients who failed

treatment was 273 days (IQR 136-643.5). There are no significant differences between the cured and failed group (p-value = 0.5586).

The influence of the duration of ART on the treatment outcomes in mono-resistance TB was not done due to insufficient data.

4.14. Comparison of the treatment outcomes in MDR-TB and mono-resistance-TB

The outcomes of MDR-TB, RMR-TB and HMR-TB are compared to see if there are any differences. The Chi-square test was used since it is a categorical variable.

Table 39: Comparison of the treatment outcomes in MDR-TB and mono-resistance-TB

Type of drug resistance	Cured	Failed	Unknown	Total
MDR-TB	104 (42.6%)	75 (30.7%)	65 (26.6%)	244
RMR-TB	42 (40.%)	21 (20.%)	40 (38.8%)	103
HMR-TB	22 (56.4%)	8 (20.5%)	9 (23.%)	39
Total	168 (43.5%)	104 (26.9%)	106 (29.5%)	386

Table 39 shows the outcomes per drug-resistance group. The cure rate was 42.6%, 40.% and 56.4% in MDR-TB, RMR-TB and HMR-TB patients respectively. There were no significant differences amongst the group (p-value = 0.049).

4.15 Comparison of the treatment outcomes in patients treated with ofloxacin and moxifloxacin containing regimen

In this section, the treatment outcomes in MDR-TB, RMR-TB and HMR-TB patients with available data who received either ofloxacin or moxifloxacin containing regimen are shown below. The Chi-square test was used since it is a categorical variable.

4.15.1 MDR-TB patients

Table 40: Comparison of the treatment outcomes in MDR-TB patients treated with ofloxacin and moxifloxacin containing regimen.

Fluroquinolones	Cured	Failed	Unknown	Total
Ofloxacin	40 (38.%)	34 (32.%)	30 (28.%)	104
Moxifloxacin	46 (46.9%)	26 (26.5%)	26 (26.5%)	98
Total	86	60	56	202

Table 40 shows the cure rate in patients treated with ofloxacin and moxifloxacin containing regimen. Of the 202 MDR-TB patients with available data, 104 and 98 patients were treated with ofloxacin and moxifloxacincontaining regimen, respectively. The cure rate was 38.% and 46.9% in patients treated with ofloxacin and moxifloxacin containing regimen, respectively. However, no significant differences or associations were found between the two groups of patients receiving either ofloxacin or moxifloxacin containing regimen (p= 0.47).

4.15.2. Rifampicin mono-resistant TB patients

Table 41: Comparison of the treatment outcomes in Rifampicin mono-resistant TB patients treated with ofloxacin and moxifloxacin containing regimen

Fluroquinolones	Cured	Failed	Unknown	Total
Ofloxacin	14 (33.3%)	12 (28.%)	16 (38.1%)	42
Moxifloxacin	27 (45.%)	9 (15.%)	23 (2%)	59
Total	41	21	39	101

Table 41 shows the cure rate in patients treated with ofloxacin and moxifloxacin containing regimen in Rifampicin mono-resistant TB patients. Of the 101 Rifampicin mono-resistant TB patients with available data, 42 and 59 patients were treated with

ofloxacin and moxifloxacin containing regimen respectively. The cure rate was 33.3% and 45.% in patients treated with ofloxacin and moxifloxacin containing regimen respectively. However, no significant differences or associations were found in the treatment outcomes between the two groups of patients receiving either ofloxacin or moxifloxacin containing regimen (p= 0.23).

4.15.3. Isoniazid mono-resistant TB patients

Table 42: Comparison of the treatment outcomes in Isoniazid mono-resistant TB patients treated with ofloxacin and moxifloxacin containing regimen

Fluroquinolones	Cured	Failed	Unknown	Total
Ofloxacin	6 (85.7%)	0 (0.0%)	1 (14.%)	7
Moxifloxacin	3 (33.3%)	4 (44.4%)	2 (22.2%)	9
Total	9	4	3	16

Table 42 shows the cure rate in patients treated with ofloxacin and moxifloxacin containing regimen in Isoniazid mono-resistant TB patients. Of the 16 Isoniazid mono-resistant TB patients with available data, 7 and 9 patients were treated with ofloxacin and moxifloxacin containing regimen respectively. The cure rate was 85.7% and 33.3% in patients treated with ofloxacin and moxifloxacin containing regimen respectively. However, no significant differences or associations were found in the treatment outcomes between the two groups of patients receiving either ofloxacin or moxifloxacin containing regimen (p= 0.077).

4.16 Influence of DR-TB localization on DR-TB treatment outcomes

This section shows the influence of DR-TB localization on the treatment outcomes in MDR-TB, RMR-TB and HMR-TB patients. The Chi-square test was used since it is a categorical variable

4.16.1. MDR-TB patients

Table 43: Influence of MDR-TB localization on MDR-TB treatment outcomes.

MDR-TB localization	Cured	Failed	Unknown	Total
Extrapulmonary TB	5 (38.%)	3 (23.%)	5 (38.%)	13
Pulmonary TB	96 (42.%)	72 (31.7%)	59 (2%)	227
Pulmonary TB and extrapulmonary TB	3 (75.0%)	-	1 (25.0%)	4
Total	104	75	65	244

Table 43 shows the influence of MDR-TB localization on the treatment outcomes amongst MDR-TB patients. As indicated in the table above, the cure rate was 38.46%, 42.% and 75.0% in patients infected with extrapulmonary TB, pulmonary TB, and in patients co-infected with pulmonary and extrapulmonary TB, respectively. However, no significant differences or association was found in the treatment outcomes amongst the 3 groups (p= 0.51).

4.16.2. Rifampicin mono- resistant TB patients

Table 44: Influence of TB localization on Rifampicin mono-resistant-TB treatment outcomes.

TB localization	Cured	Failed	Unknown	Total
Extrapulmonary TB	0 (0.0%)	2 (50.0%)	2 (50.0%)	4
Pulmonary TB	41(41.8%)	19 (19.%)	38 (38.%)	98
Pulmonary TB and extrapulmonary TB	-	-	-	-
Total	41	21	40	102

Table 44 shows the influence of TB localization on the treatment outcomes amongst Rifampicin mono-resistant TB patients. As indicated in the table above, of the 102

Rifampicin mono-resistant TB patients with available data, 98 patients were infected with pulmonary TB, 4 patients had extrapulmonary TB and no patients were co-infected with pulmonary and extrapulmonary TB. The cure rate was 41.8% in patients infected with pulmonary TB and 0% in patients infected with extrapulmonary TB. However, no significant differences or association was found among the treatment outcomes among the 3 groups (p-value = 0.11). There were insufficient data to compare the 3 groups.

4.16.3. Isoniazid monoresistant TB

Table 45: Influence of TB localization on Isoniazid mono-resistant-TB treatment outcomes.

TB localization	Cured	Failed	Unknown	Total
Extrapulmonary TB	2 (100%)	0 (0.0%)	0 (0.0%)	2
Pulmonary TB	20 (54.%)	8 (21.6%)	9 (24.3%)	37
Pulmonary TB and Extrapulmonary TB	-	-	-	-
Total	22	8	9	39

Table 45 shows the influence of TB localization on the treatment outcomes amongst Isoniazid mono-resistant TB patients. As indicated in the table above, the cure rate was 54.% and 100% in patients infected with pulmonary TB and patients infected with extrapulmonary TB. However, no significant differences or association was found between the 2 groups (p-value = 0.495).

CHAPTER FIVE: DISCUSSION

The aim of this study was to investigate and describe the sputum culture conversion time in HIV-positive and HIV-negative patients with multidrug resistant TB (MDR-TB), Rifampicin mono-resistant TB (RMR-TB) and Isoniazid mono-resistant TB (HMR-TB). There are very few studies in the available literature that have shown the influence of HIV infection on the time to sputum culture conversion in these groups of patients. This study also aimed to investigate whether inappropriate (i.e. low and high) anti-TB drug dose could affect the time to sputum culture conversion in these groups of patients.

The influence of antiretroviral duration, immunological and virological profile, sputum culture conversion time, DR-TB localization and the replacement of ofloxacin by moxifloxacin were assessed on the treatment outcomes in these groups of patients. In addition, the treatment outcomes of MDR-TB, RMR-TB and HMR-TB were compared to see if there are any differences.

We were able to successfully fulfil all of our specific objectives as outlined at the beginning of this study, on the basis that previous authors had found evidence of similar sputum culture conversion time in HIV-positive and HIV-negative MDR-TB patients, and that HIV infection does not influence the time to sputum culture conversion. It was observed in this study that treatment outcomes were statically significantly worst for HIV-positive patients with MDR-TB and HIV-negative patients with HMR-TB. In addition, inappropriate (i.e. low and high) anti-TB drug dose does not have any influence on the time to sputum culture conversion in MDR-TB, RMR-TB and HMR-TB patients respectively. It was observed in this study that MDR-TB, RMR-TB and HMR-TB patients who received any inappropriate anti- TB drug dose (i.e. low and high) had the worst survival rate.

5.1. Demographics, clinical characteristics, and treatment outcomes of patients included in this study

5.1.1. The number of patients included in this study

Three hundred and eighty-six (57.51% males and 42.49% females) patients included in this study were to describe the influence of microbiological parameters on the treatment outcomesin patients infected with MDR-TB, RMR-TB and HMR-TB respectively. In addition, the number of patients in HIV-positive and HIV-negative groups was sufficient to give a power of about 80% in detecting a statistical significant difference in the means of about 1.96 standard deviations based on our power calculations. Also, the number of patients included in previously published studies was similar to the number of patients in our study.

Studies of same nature have used similar sample sizes to detect a significant change in their measurements. For example, a study by Satti et al (2012) that investigated the outcomes of MDR-TB treatment with early initiation of ART in HIV- positive patients in Lesotho included 134 patients. Mukinda et al (2012) who investigate the rise of Rifampicin mono-resistant TB in the Western Cape in South Africa included 91 patients. Holtz et al (2006), Brust et al (2011), and Hafkin et al (2013) used a sample size of 167, 45, and 70 patients in their respective studies to determine the sputum culture conversion time in MDR-TB patients. Based on the number of patients in previous studies, our sample size of 244 MDR-TB patients, 103 Rifampicin mono-resistant TB and 39 Isoniazid mono-resistant TB was sufficient to determine the microbiological parameters influencing treatment outcomes in patients with MDR-TB, RMR-TB, HMR-TB and in those with MDR-TB, RMR-TB, HMR-TB co-infected with HIV respectively.

5.2. Treatment outcomes

5.2.1. Multidrug resistant tuberculosis patients

Several investigators from different countries have reported successful treatment outcomes of about 48%- 64% in MDR-TB patients (Johnston et al., 2009; Orenstein et al., 2009; Ahuja et al., 2012; Marais et al., 2013). Although for these studies successful treatment was defined as a combination of cure and treatment completed. The total MDR-TB cure rate found in this study (4%) is higher than the cure rate reported in a study conducted in South Africa (36%) by Mugabo et al (2015). These findings are consistent with MDR-TB cure rates reported at national level (30-50%) in patients without HIV –

infection in South Africa (DOH, 2013). The total failure rate in MDR-TB patients is 3% which is high as compared to other studies conducted in South Africa where failures rates ranges between 2.5% to 17% among MDR-TB patients (Brust et al., 2010; Farley et al., 2011; Marais et el., 2013). Although in this study, failure rate and mortality were combined as one outcome (failure).

In this study, a high proportion of unknown outcomes (2%) in MDR-TB patients was noted. Three meta-analysis studies on MDR-TB outcomes reported 13%, 23%, and 11% default rate (Johnston et al., 2009; Orenstein et al., 2009; Ahuja et al., 2012). This study finding is consistent with other studies conducted in South Africa that reported default rates ranging between 20 and 29% (Shean et al., 2008; Farley et al; 2011; Marais et al., 2013).

5.2.2. Rifampicin mono-resistant TB patients

The treatment outcomes of Rifampicin mono-resistant TB have not been deeply studied as compared to MDR-TB, which is well known to be associated with poor treatment outcomes. Although few studies have reported worst treatment outcomes such as treatment failure and mortality in RMR-TB patients (Mukinda et al., 2012; Prach et al., 2013; Schnippel et al., 2015; Villegas et al., 2016). Studies from France and Europe have reported high cure rates of 67% and 70.8% in RMR-TB patients (Meyssonnier et al., 2014; Villegas et al., 2016) as compared to the total cure rate found in this study (40.%). This study finding is consistent with a study conducted in South Africa that reported a 33.7% cure rate in RMR-TB patients (Schnippel et al., 2015). in this study was as a result of the high-unknown in this group of patients.

The total failure rate in RMR-TB patients found in this study was 20.%, which is lower as compared to the failure rate reported by studies conducted in South Africa (36.8%) and France (33%) (Meyssonnier et al., 2014; Schnippel et al., 2015). The total unknown outcome in RMR-TB patients found in this study was 38.8%. This is consistent with a study conducted in South Africa that reported unknown rates of 51.4% (Schnippel et al., 2015). Another study from Europe reported a 20.83% unknown rate (Villegas et al., 2016). The unknown rate is high and factors influencing it need to be investigated.

5.2.3. Isoniazid mono-resistant TB patients

Isoniazid mono-resistance treatment outcomes have been a topic of debate due to conflicting studies. Investigators have reported high cure rate in Isoniazid mono- resistant TB (HMR-TB) patients from the United States of America (71%) and Europe (74.1%) (Gegia et al., 2012; Villegas et al., 2016).Our results were compatible with previous reports demonstrating that Isoniazid mono-resistant cases are at a higher risk for poor outcomes, specifically failures and deaths. The total cure rate found in this study (56.4%) is lower than that reported in a study conducted in South Africa by Jacobson et al. (2011) (65%).

The failure rate found in this study (20.5%) is comparable to those reported in South Africa by Jacobson et al. (2011), who reported a 16% failure rate. Studies from the United States of America and Europe reported failure rates ranging between 2%-8% in HMR-TB patients (Cattamanchi et al., 2009; Bang et al., 2010; Villegas et al., 2016). This study finding is consistent with a meta-analysis study that reported failure rates of between 18%-44% in HMR-TB patients (Menzies et al., 2009). The unknown outcomes in HMR-TB patients found in this study (23.%) is high as compared to those reported in South Africa 16% and Europe 18.82% (Jacobson et al., 2011; Villegas et al., 2016).

5.3. Effect of age group and sex distribution on treatment outcomes.

5.3.1. MDR-TB patients

The cure rate was high in patients in the age range 20 years and below (69.2%), as compared to patients in the age range 21-30 years (44.%), 31-40 years (42.1%), 41-50 years (40.0%), and those above 50 years' age range (35.%).

Although there are no differences among the treatment failure rate in MDR-TB patients by age range. The failure rates are high in patients in the 21-30 years range (30.5%), 31-40 years (2%), 41-50 years (35.%), and those above 50 years' age range (35.%) only

patients in the age range 20 years and below had a low failure rate (7.%). However, these rates are unacceptably high and the risk factors associated with them need to be investigated. This study finding is consistent with studies conducted in South Africa and Lesotho that reported poor outcomes in MDR-TB patients in the age range 31-40 years and 41-50 years (Seung et al., 2009; Brust et al., 2010). These high failure rates may also be attributed to the high prevalence of HIV infection among these age group, as the association between HIV infection and MDR-TB mortality and failure has been reported by several studies (Flament-Saillour et al., 1999; Kliiman and Altraja, 2009; Seung et al., 2009; Brust et al., 2010; Farley et al., 2011). Why failure rate among the older age group (above 50 years and older) may be attributed to advanced age, increased co-morbidies, overall physiological deterioration, and difficulty in accessing several healthcare opportunities along with increasing age (Vasankari et al., 2007; Babalik et al., 2013).

The unknown outcomes are high in all age groups; it ranges within 23.% to 29.0%. This high unknown outcomes may be explained by high HIV infection, as MDR-TB and/ HIV co-infection is amongst the condition related factors reported as predictors of MDR-TB treatment default (Brust et al., 2010). However, there have been other studies that found no link between HIV infection and MDR-TB treatment default (Shean et al., 2008; Farley et al., 2011).These suggest that there may have been other factors which contributed to that high-unknown rate. A meta-analysis study reported that patients who default on treatment were more likely to be older people (Ahuja et al., 2012). Other investigators who conducted a study on the evaluations of MDR-TB treatment default in South Africa revealed that healthcare workers' attitude and substance abuse are associated with patient default (Holtz t al., 2006).

Similarly, sex did not have any influence on the treatment outcomes in MDR-TB patients. The cure rate was almost similarin male (41.8%) and female cases (43.%), thus indicating that sex is not a predictor of poor treatment outcomes in MDR-TB. Although studies conducted in South Africa had shown that male and female sex are associated with poor treatment outcomes (Brust et al., 2010; Farley et al., 2011; Marais et al., 2013). However, this study rules out sex as a factor influencing MDR-TB treatment outcomes.

5.3.2. Rifampicin mono-resistant TB patients

It was shown in the previous section that there are no differences in the treatment outcomes among RMR-TB patients by age range. Poor cure rate was observed in all age groups, ranging between 38.% to 43.%, except patients in the age group 20 years and below, due to no data. The failure rate was high among patients in the age range 20 years and below (50%), 21-30 years (26.%), 41-50 years (18.%), and those above 50 years' age range (38.%) as compared to patients in the age range 31-40 years (9.%). However, these rates are unacceptably high and the risk factors associated with them need to be investigated. These high failure rates may also be attributed to the high prevalence of HIV infection among these groups, as the association between HIV infection and RMR-TB has been reported by several studies from South Africa, France, United States of America, and Europe (Munsiff et al., 1997; Sandman et al., 1999; Mukinda et al., 2012; Prach et al., 2013; Meyssonnier et al., 2014).

The unknown outcomes are high in all age groups ranging between 23.0% -50%. This high unknown outcome may be explained by high HIV infection, as RMR-TB and/ HIV co-infection are amongst the condition related factors reported as predictors of RMR-TB treatment default (Mukinda et al., 2012). However, these rates are unacceptably high and the risk factors associated with them need to be investigated.

Similarly, sex did not have any influence on the treatment outcomes in Rifampicin mono-resistant TB patients. The cure rate was almost similar in male (38.6%) and female (43.%) cases, thus indicating that sex is not a predictor of poor treatment outcomes in Rifampicin mono-resistant TB patients. Although a study conducted in South Africa had shown that male gender was associated with RMR-TB and in that study poor treatment outcomes such as failure were reported (Mukinda et al., 2012).

5.3.3. Isoniazid mono-resistant TB patients

There are no differences in the treatment outcomes among the different age range in HMR-TB patients. The cure rate was high in patients in the age range 20 years and

below (100%), 41-50 years' age range (72.7%) and those above 50 years' age range (66.7%) as compared to patients in the age range 21- 30 years (33.3%) and 31-40 years' age range (41.7%). This study finding is consistent with a study conducted in South Africa that reported a better cure rate for patients in the age range 44-67 years (Jacobson et al., 2011).

There are no differences among the treatment failure rate in Isoniazid mono- resistant TB patients by age group. The failure rates are high for patients in the age range 21-30 years (33.3%), 31-40 years (16.7%) and those in the 41-50 years' age range (27.%) as compared to patients in the age range 20 years and below (0%) and those above 50 years' age range (0%). This study finding is consistent with a study conducted in South Africa that reported worst treatment outcomes for HMR-TB patients in the age range 33-43 years (Jacobson et al., 2011). The authors reported that poorer compliance and default were the reason why the treatment outcomes were worse in this group of patients.

The unknown outcomes are high for patients in the age range 21-30 years (33.3%), 31-40 years (41.7%) and those above 50 years' age range (33.3%) as compared to patients in the age range 20 years and below (0%) and those in the age range 41-50 years (0%). However, these rates are unacceptably high and the risk factors associated with them need to be investigated.

Similarly, sex did not have any influence on the treatment outcomes in Isoniazid mono-resistant TB patients. The cure rate in male (57.9%) and female (55.0%) cases was almost similar, thus indicating that sex is not a predictor of poor treatment outcomes in Isoniazid mono-resistant TB patients. This study finding is similar to a study conducted in South Africa that found no link between sex and poor treatment outcomes in HMR-TB patients (Jacobson et al., 2011).

5.4. Effect of HIV infection and ART on treatment outcomes

5.4.1. MDR-TB patients

Previous studies have reported high mortality and poor treatment outcomes associated with HIV-infected patients (Flament-Saillour et al.1999; Kliiman and Altraja 2009; Brust et al.2010; Ekaterina et al., 2012). The poor outcomes and especially rapid time to death have mostly been observed in the absence of effective antiretroviral treatment (Gandhi et al. 2006; Wells et al. 2007; Seung et al. 2009). A previous study from KwaZulu-Natal Province, the first extensive study detailing the treatment outcomes of MDR-TB patients in a TB referral hospital in South Africa, reported an association between HIV co-infection and death. Since the study period was prior to the availability of ART therapy in the public sector (2000-2003), the authors attributed the HIV/death association to the lack of ART therapy and recommended an integration of ART with second-line anti-TB treatment in the management of MDR-TB patients (Brust et al.2010). Although more recent studies from South Africa have revealed that HIV infection does not influence the treatment outcomes in MDR-TB patients (Farley et al., 2011; Brust et al., 2012; Marais et al., 2013; Mugabo et al., 2015). The current study showed no association between HIV status and poor treatment outcomes.

The cure rate found in HIV-positive patients (40.%) and HIV-negative patients (59.6%) with MDR-TB is higher than that reported by a study conducted in South Africa (Mugabo et al., 2015). The authors reported cure rate of 35% in HIV-positive and 37% in HIV-negative MDR-TB patients. Another study conducted in South Africa by Farley et al (2011) reported a cure rate of 40% in HIV-positive patients and 49.6% in HIV-negative patients. Although in this study, the cure rate in HIV-positive patients was lower as compared to HIV-negative patients with MDR-TB due to a high-unknown rate. This study finding is similar to other studies conducted in South Africa that found no differences or associations in the cure rate between HIV-positive and HIV-negative patients with MDR-TB (Faley et al., 2011; Mugabo et al., 2015).

There were no differences between the treatment failure rate in HIV-negative patients (37.%) and (26.2%) in HIV-positive patients with MDR-TB. The failure rates found in this study are high as compared to a study conducted in South Africa by Mugabo et al., (2015) (9%) in HIV-negative patients with MDR-TB and (5%) in HIV-positive patients with MDR-TB. Another study conducted in South Africa reported failure rate of 4.2% in

HIV-positive patients and 13.2% in HIV-negative patients with MDR-TB (Farley et al., 2011).

There are no differences between the unknown outcomes in HIV-negative patients (20.2%) and in HIV-positive patients with MDR-TB (31.0%). However, these rates are unacceptably high and the risk factors associated with them need to be investigated. In a study conducted in South Africa, Mugabo et al (2015) reported a default rate of (20%) and (25%) in HIV-negative MDR-TB patients and HIV-positive patients with MDR-TB.

It was shown in this study that HIV infection does not influence MDR-TB treatment outcomes. There were no data for HIV-positive patients with MDR-TB not receiving antiretroviral therapy in this study, so we could not compare the cure rate in HIV-positive patients on ART and HIV- positive patients not on ARVs. The cure rate in HIV-positive patients receiving ART (41.%) is high as compared to the cure rate reported in a study conducted in South Africa (35%) (Mugabo et al., 2015).Although the authors reported no differences in the treatment outcomes between HIV-positive patients receiving ART and HIV-positive patients not on ART (Mugabo et al., 2015).We could not compare this group because of insufficient data.

The failure rate in HIV-positive patients receiving ARVs is high (38.9%). A study conducted in South Africa reported a failure rate of 65% in HIV-positive patients receiving ARVs (Mugabo et al., 2015). These rates are high, and one could expect lower failure rates, although a previous study has shown that receiving ART was not associated with improved survival in HIV-infected MDR-TB patients (Ghandi et al., 2012). We could not compare the failure rates in HIV- positive patients receiving ART and HIV-positive patients not receiving ART because of insufficient data.

The unknown rate is high (19.4%) in HIV-positive patients receiving ARVs (19.2%) as well as HIV-positive patients not on ARVs (100%).

5.4.2. Rifampicin mono-resistant TB patients

We found no differences in the cure rate between HIV-negative (41.8%) and HIV-positive patients with RMR-TB (40.%). This study finding is consistent with a study conducted in France by Meyssonnier et al. (2014), that found no differences in the cure rate between HIV-positive and HIV-negative patients with RMR-TB. There are no differences between the treatment failure rate in HIV-negative patients (25.%) and (15.%) in HIV–positive patients with RMR-TB. Although HIV-negative patients tend to have a higher failure rate as compared to HIV-positive patients with RMR-TB. This study finding is consistent with studies conducted in South Africa, United States of America, Europe and France that reported RMR-TB to be linked or associated with poor treatment outcomes such as failure and death (Mukinda et al. 2012; Prach et al. 2013; Meyssonnier et al., 2014; Villegas et al., 2016).

Although no difference was found between the unknown outcomes in HIV-positive and HIV- negative patients with RMR-TB, the unknown outcome in HIV-positive patients (44.2%) is high as compared to HIV-negative patients with RMR-TB (33.3%). However, these unknown outcomes are unacceptably high and the risk factors associated with them need to be investigated. A study conducted in South Africa has reported RMR-TB to be linked with default (Mukinda et al., 2012).

The cure rate in HIV-positive patients with RMR-TB on antiretroviral therapy (40.8%) was low as compared to HIV-positive patients with RMR-TB not on antiretroviral therapy (50%). Although there are no differences in the cure rates between the two groups of patients. Our findings could not be compared with other studies because no previous studies have looked at the influence of ART history on the cure rate in RMR-TB patients.

The failure rate was high in HIV-positive patients with RMR-TB on antiretroviral therapy (14.%) as compared to HIV-positive patients with RMR-TB not on antiretroviral therapy (0%). One would expect RMR-TB patients on ARVs to benefit from the protective effects of ART. More studies are needed to look at the impact on ARVs on the treatment outcomes in RMR-TB patients.

The unknown outcome was high in HIV-positive patients with RMR-TB receiving ARV (44.9%) and patients with RMR-TB not on antiretroviral therapy (50%). These rates are high and the factors influencing them need to be investigated.

5.4.3. Isoniazid mono-resistant TB patients

This study does not show any significant differences between the cure rate in HIV-positive (64.%) and HIV-negative patients with HMR-TB (52.0%). Although HIV-negative patients with HMR-TB had a lower cure rate as compared to HIV-positive patients with HMR-TB. This study finding is consistent with a study conducted in South Africa that found no differences in the treatment outcomes between HIV-positive and HIV-negative patients with HMR-TB (Jacobson et al., 2011). There are no differences between the treatment failure rate in HIV-negative patients with HMR-TB (28.%) and (7.1%) in HIV–positive patients with HMR-TB. Although HIV- negative patients had a higher failure rate as compared to HIV-positive patients. There are no differences between the unknown rate in HIV-negative patients with HMR-TB (20%) and HIV-positive patients with HMR-TB (28.%).

It was shown that the cure rate was 64.% in HIV-positive patients with HMR-TB on antiretroviral therapy. There were insufficient data in the HIV-positive patients with HMR-TB not receiving antiretroviral therapy. We could not compare the treatment outcomes in this group of patients.

5.5. Influence of previous anti-tuberculosis treatment on treatment outcomes

5.5.1. MDR-TB patients

There are no differences among the treatment outcomes in new patients (38.9%), previously treated patients for TB (37.8%) and previously treated patients for MDR-TB (47.%). Cure rate was poor in new patients with MDR-TB due to high failure rate, as

well as patients previously treated for TB. This study finding is inconsistent with a meta-analysis study that reported successful treatment outcomes in new MDR-TB patients (Johnston et al; 2009).

The failure rate in new MDR-TB patients (42.%) is high as compared to patients previously treated for TB (25.%) and patients previously treated for MDR-TB (28.%). This study finding is consistent with several studies that have demonstrated repeatedly that a history of previous TB infection and previous TB treatment were associated with poor treatment outcomes such as failure and death in MDR-TB patients (Faustini et al., 2006; Johnston et al., 2009; Kliiman and Altraja, 2009; Dheda et al., 2010; Brust et al., 2010).

The unknown outcomes are high in patients previously treated for TB (37.3%), as compared to patients previously treated for MDR-TB (24.%) and new MDR-TB patients (18.5%). Factors influencing them need to be investigated.

5.5.2. RMR-TB patients

From the previous section, it was shown that there is an association between previous TB treatment and poor treatment outcomes in RMR-TB patients. The cure rate was poor (36.%) in patients previously treated with anti-TB drugs as compared to new RMR-TB patients (53.%). The failure rate in new RMR-TB patients (26.9%) is higher, as compared to previously treated RMR-TB (18.%). This study finding is inconsistent with a study conducted in France that reported higher failure rate in previously treated patients with RMR-TB, as compared to new patients with RMR-TB (Meyssonnier et al., 2014). The authors reported failure rate of 50% in previously treated patients and 19% in new patients.

The unknown outcome in previously treated patients with RMR-TB (45.%) is high as compared to new patients (19.2%) These rates are very high, most especially in the previously treated patients with RMR-TB. A study conducted in South Africa has reported an association between RMR-TB patients and default after previous TB treatment (Mukinda et al., 2012). Factors influencing this high-unknown outcomes needs

to be investigated.

5.5.3. Isoniazid mono-resistant TB patients

As highlighted earlier, there are no differences in the cure rate between new and previously treated patients with Isoniazid mono-resistant TB. The cure rate in new patients (53.%) was almost similar to HMR-TB patients previously treated with anti-TB drugs (57.%). This study finding is inconsistent with studies from Europe that reported a cure rate of 76% in new and 58% in previously treated patients with HMR-TB (Gegia et al., 2012).

The failure rate in new patients (30.%) was high, as compared to patients previously treated with HMR-TB (15.%). This study finding is in contrast with a study conducted in South Africa that found no link between new TB treatment and poor treatment outcomes (Jacobson et al., 2011). Some other investigators have demonstrated repeatedly that a history of previous TB infection and previous TB treatment were associated with poor treatment outcomes, such as failure and death in cases of Isoniazid mono-resistant TB (Gegia et al., 2012; Wang et al., 2014).

The unknown outcome in previously treated patients with HMR-TB (26.9%) is high as compared to new patients with HMR-TB (15.%). A study has revealed that patients with a history of previous TB treatment may be more likely to default from treatment, particularly when given a regimen of a longer duration (Gegia et al., 2012). They reported a treatment default rate of 20.6 % in HMR-TB patients.

5.6. Influence of diagnostic category on treatment outcomes

5.6.1. MDR-TB patients

It was shown in the results section, that there is a significant association between patients' diagnostic category and treatment outcomes in MDR-TB patients. The cure rate was low in new cases (39.6%), as compared to retreatment cases, after transfer cases

(66.7%),after default (42.1%), after relapse (45.%), after failure (44%) and other cases (12.5%),due to higher failure and unknown rate. This suggests that previous exposure to anti-TB drugs is not the main reason why MDR-TB treatment outcomes are poor, because in this study new cases also had a poor cure rate.

The failure rates are high in new cases (43.4%), after failure cases and other cases (50%), as compared to the other retreatment cases that range between 23.9% and 33.3%. This shows that new MDR-TB cases are more likely to have poor treatment outcomes. The study finding disagrees with a study conducted in South Africa that showed no link between poor treatment outcomes in new cases and retreatment cases in MDR-TB patients (Marais et al., 2013). These failure rates are high and factors influencing them need to be investigated.

These unknown outcomes are high in the retreatment cases (ranges between 28% to 37.5%), as compared to new cases (1%). The causes of these high unknownoutcomes,and the factors influencing, them need to be investigated.

5.6.2. Rifampicin mono-resistant TB patients

It was shown that there are no significant differences between the treatment outcomes in RMR-TB patients with new cases and retreatment cases. The cure rate was poor in after default cases (26.7%) and after relapse cases (35.9%) as compared to new cases (50%), after failure cases (55.6%) and after transfer cases (100%). The failure rate is high in new cases (30.77%), as compared to after default (20%), after relapse (1%) and after failure cases (11.1%). The study finding agrees with a study conducted in South Africa and Europe that showed a link between poor treatment outcomes and retreatment cases in Rifampicin mono-resistant TB patients (Mukinda et al., 2012; Meyssonnier et al., 2014).

The unknown outcomes are very high in after default cases (53.3%), after relapse cases (46.15%) and after failure cases (33.3%), as compared to new cases (19.2%). These rates are unacceptably high and factors influencing them need to be investigated.

5.6.3. Isoniazid mono-resistant TB patients

There are no significant differences between the treatment outcomes in HMR-TB patientscases, new and retreatment. The cure rate is high in after default cases (71.4%) as compared to new cases (53.8%), after relapse (50%) and after failure cases (60%). The failure rates are high in new cases (30.%), as compared to after default cases (14.%), after relapse cases (14.%) and after failure case (20%). The number of patients in each of the diagnostic categories was low. This study finding agrees with a study conducted in the United States of America over a 3 years period (2007-2009) that reported a link between poor treatment outcomes and retreatment patients with HMR-TB (Gegia et al., 2012).

The unknown outcomes are high in after relapse (35.7%) and after default (20%) cases, as compared to new cases (15.%) and after default cases (14.%). These rates are high, especially in after relapse cases. The factors contributing to thesehigh unknownoutcomes need to be investigated.

5.7. Influence of CD4 count and viral load at baseline on treatment outcomes in HIV- positive patients

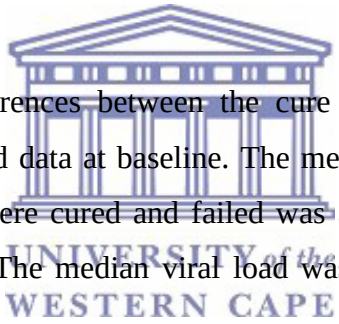
5.7.1. MDR-TB patients

It was shown in the previous section (Table 36) that there are no significant differences between the cured (22 patients) and failed (17 patients) group of HIV-positive patients with available CD4 count data. The median CD4 count in HIV-positive patients with MDR-TB who were cured and failed was 230 (IQR 75-465) and 207 (IQR 119-279) respectively, and treatment outcomes did not differ between the cured and failed group of HIV-positive patients with MDR-TB. This study findingis inconsistent with a study conducted in KwaZulu-Natal, South Africa during a 2-year period (2005-2006), that reported a CD4 count less than 50 cells/mm^3 and CD4 count of 51-200 cells/mm^3 to be associated with poor treatment outcomes such as mortality(Gandhi et al., 2012). This study finding is in line with another study conducted in Gauteng, South Africa,during a 4 –year period (2007-2010), that reported a higher cure rate in MDR-TB patients with CD4 counts of 201-349 cells/mm^3 and CD4 counts of >350 cells/mm^3 (Umanah et al., 2015).This study finding rules out a CD4 count at baseline as a possible factor that influences MDR-TB treatment outcomes.

There are no significant differences between the cure rate and failure rate in HIV-positive patients with a viral load data at baseline. The median viral loads in HIV-positive patients who were cured and failed was 40 (IQR 40 -1507.50) VL and 1430 (IQR 421-3300) respectively. The median viral load was higher in the failed group as compared to the cured group.

5.7.2. Rifampicin mono-resistant-TB patients

It was shown in (Table 37) that there are no significant differences between the cured and failed group of HIV-positive patients with RMR-TB with available CD4 count data. Although no significant differences are seen, the median CD4 count was low in the failed group 107 (IQR 7-207) as compared to the cured group of RMR-TB patients 308 (IQR 111-338).



There are no significant differences between the cure rate and failure rate in HIV-positive patients with viral load data at baseline. The median viral load in HIV-positive patients with RMR-TB who were cured and failed was 58 (IQR 40 -76) VL and 1430 (IQR 421-3300) respectively. The median viral load was higher in the failed group as compared to the cured group.

Although a study conducted in South Africa hadreported RMR-TB patients to be associated with a low CD4 count (Mukinda et al., 2012). It was difficult to compare this result because no previous studies had reported the influence of CD4 count and viral load at baseline on the treatment outcomes in RMR-TB patients.

5.7.3. Isoniazid mono-resistant TB patients

It was difficult to compare our results in this group of patients because of insufficient data.

5.8. Effects of inappropriate (low) anti-TB drug dose on treatment outcomes.

5.8.1. MDR-TB patients

As highlighted earlier there is evidence to suggest that MDR-TB patients who had poor treatment outcomes might be subject to sub-therapeutic plasma levels of anti-TB drugs, possibly as a result of low anti-TB drug dose. Although no significant differences were observed between MDR-TB patients who received any low anti-TB drug dose and MDR-TB patients who did not receive any low anti-TB drug dose. The cure rate was worst in MDR-TB patients who received any low anti-TB drug dose (20.00%), due to high failure (33.3%) and unknown rate (46.7%), as compared to MDR-TB patients that did not receive any low anti-TB drug dose (37.6%). The failure rate (33.3%) and unknown outcome (46.7%) in MDR-TB patients who received any low anti-TB drug dose was high. These study findings confirm the understanding that a previous study from the United States of America conducted in 2005 has shown, that low serum concentrations of anti-TB drugs may be related to poor clinical outcomes, which are closely related to treatment failure in human immunodeficiency virus (HIV) infected and non-HIV infected patients (Weiner et al., 2005). Another investigator believed that low serum concentration of anti-TB drugs may be related to poor clinical outcomes (Peloquin et al., 1999). Since some patients in this study received suboptimal anti-TB drug dosage this could be one of the factors affecting the treatment outcomes in MDR-TB patients.

5.8.2. Rifampicin mono-resistant-TB patients

It was shown that there are no differences between the cured and failed group of RMR-TB patients who received any low anti-TB drug dose. The cure rate in RMR-TB patients who received any low anti-TB drug dose was almost similar (37.5%) to the RMR-TB cure rate in patients who did not receive any low anti-TB drug dose (33.3%). The failure rate in RMR-TB patients who received any low anti-TB drug dose was high (37.5%), as

compared to RMR-TB patients who did not receive any low anti-TB drug dosage (14.8%). The unknown outcome was high in RMR-TB patients who did not receive any low anti-TB drug dose (51.%), as compared to RMR-TB patients who received any low anti-TB drug dose (25%). Since poor treatment outcomes were seen in this study, we believe low anti-TB drug dose had an effect on the treatment outcomes in RMR-TB patients.

5.8.3. Isoniazid mono-resistant TB patients

HMR-TB patients did not receive any low anti-TB drug dose**.**

5.9. Determination of time to sputum culture conversion in DR-TB patients

5.9.1. MDR-TB patients

Our findings were favorable, demonstrating that nearly all MDR-TB patients (96%) achieved culture conversion within the first six months of treatment, irrespective of HIV status. Moreover, the culture conversion time for HIV co-infected patients was similar to reports of HIV-negative patients in the published literature. (Seung et al., 2009; Brust et al., 2011; Hafkin et al., 2013). This study finding is similar to other studies conducted in Southern Africa. In a study conducted in Lesotho, culture conversion was documented in 68% of 76 study patients after a follow up of 252 days (Seung et al., 2009). Brust et al (2011) documented a culture conversion rate of 88% in the 45 patients in Tugela Ferry South Africa, and they found no difference in the time to sputum culture conversion between HIV-positive patients and HIV–negative patients at the end of 6 months of treatment. Another study from Botswana, (Hafkin et al, 2013) documented a culture conversion rate of 51% of the 70 patients involved in the study. They found no difference in the proportion of patients that converted, based on HIV status at the end of 6 months of treatment. Possible reasons as to why our culture conversion was higher than in the three other Southern African studies referred to arethat our sample was far larger.

In this study, we found culture conversion rates to be similar between HIV-positive (9%) and HIV-negative patients (95%). Ten MDR-TB patients (6 HIV- positive and 4 HIV-negative) remained persistently culture-positive (i.e., in jeopardy of becoming a treatment failure). This study finding is similar to other studies conducted in Southern Africa. The finding is almost similar to a study conducted in Tugela Ferry, South Africa, that documented a culture conversion rate of 85% in HIV-positive patients and 100% in HIV-negative patients atthe end of 6 months of treatment (Brust et al., 2011). Another study conducted in Botswana documented a culture conversion rate of 50% in HIV-positive patients and 53% in HIV-negative patients at the end of 6 months of treatment (Hafkin et al., 2013).

The p-value shows that there are no significant differences in the time to sputum culture conversion between HIV positive and HIV-negative MDR-TB patients. This study finding is consistent with studies conducted in Tugela Ferry, South Africa, during a 2-year period (2008 -2009), and Botswana during a 5-year period (2005-2009) that found no differences in the time to sputum culture conversion between HIV-positive and HIV-negative patients with MDR-TB. Our high rates of culture conversion add to those recently reported amongMDR-TB/ HIV co-infected patients in South Africa (Brust et al., 2011).

5.9.2. Rifampicin mono-resistant TB patients

Our findings are favorable, demonstrating that all RMR-TB patients (100%) achieved culture conversion within the first six months of treatment, irrespective of HIV status. These early data provide optimism that a strategy of concurrently treating DR-TB and HIV may lead to favorable outcomes for co-infected patients. In this study, we found culture conversion rates to be similar between HIV-positive and HIV-negative RMR-TB patients. No patients remained persistently culture-positive (i.e. in jeopardy of becoming a treatment failure).

The p-value shows that there are no significant differences in the time to sputum culture conversion between HIV-positive and HIV-negative RMR-TB patients. This study

finding is inconsistent with a study conducted in the United States of America that reported longer time to sputum culture conversion in RMR-TB patients (Prach et al., 2013). The authors reported a median time of 93.5 days (IQR 42-162) in RMR-TB patients. The study was conducted during a 16- year period (1993 -2008), and the authors documented culture conversion in 77.1% of the 178 RMR-TB patients involved in the study. Although in that study HIV infection was not investigated. The authors compared RMR-TB, HMR-TB, MDR-TB and drug-sensitive cases. In another study from the United States of America, culture conversion was documented in 50% of the 11 RMR-TB patients (LoBue and Moser, 2005). Another study from the United States of America during a 16-year period (1993- 2008) documented culture conversion in 77.1% of the 160 RMR-TB patients involved in the study (Prach et al., 2013).

5.9.3 Isoniazid mono-resistant TB patients

Our findings were favorable, demonstrating that nearly all Isoniazid mono- resistant TB patients (97%) achieved culture conversion within the first six months of treatment, irrespective of HIV status. In this study, we found culture conversion rates to be similar between HIV-positive and HIV-negative patients with Isoniazid mono-resistant TB. Only 1 HIV-negative patient remained persistently culture-positive. This study finding is consistent with a study from Taiwan conducted during an8-year (2004- 2011)that found culture conversion in 73.7% of 395 study patientsexamined (Chien et al., 2015).Another study conducted during a 10-year period (1993 - 2002) in the United States of America, showed culture conversion in 72% of the 287 HMR-TB patients examined (LoBue and Moker, 2005).Similarly, another study conducted in the United States of America during a 16-year period (1993- 2008)showed culture conversion in 82.9% of the 3434 HMR-TB patients examined(Prach et al., 2013).

The p-value shows that there are no significant differences in the time to sputum culture conversion between HIV positive and HIV-negative HMR-TB patients. This study is inconsistent with a study conducted in the United States of America that reported longer time to sputum culture conversion in HMR-TB as compared to drug-sensitive cases (Prach et al., 2013), although in that study HIV infection was not investigated.The

authors compared HMR-TB, RMR-TB, MDR-TB and drug sensitive cases. They reported that the median time to sputum culture conversion was 48 days (IQR 26-84) in HMR-TB patients, which was almost similar to the median time to sputum culture conversion in HMR-TB-negative patients in this study of 48 days (IQR 28-103).

5.10. Influence of the sputum culture conversion time on treatment outcomes

5.10.1. MDR-TB patients

Although the sputum culture conversion rate was higher in the first 6 months of treatment in both HIV-positive and HIV-negative MDR-TB patients,the cure rate was low (40.%) in HIV-positive patients as compared to HIV-negative patients with MDR-TB (59.6%). It was observed that 37.% of HIV-positive patients and 26.2% of HIV-negative patients with MDR-TB failed treatment, even with the high rate of initial sputum culture conversion at the end of the intensive phase of treatment. The p-value (0.001) in HIV-positive patients shows that treatment outcomes were statistically significantly worse for HIV-positive patients with MDR-TB, despite early sputum culture conversion. This could suggest that early (microbiological outcome) sputum culture conversion does not suggest early clinical recovery. This study is consistent with a study conducted in Lesotho that revealed poorer treatment outcomes despite early sputum culture conversion in MDR-TB patients (Seung et al., 2009).

5.10.2. Rifampicin mono-resistant TB patients

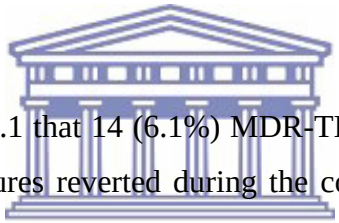
It was shown in Table 30 that the sputum culture conversion rate was higher in the first 6 months of treatment in both HIV-positive and HIV-negative RMR-TB patients. The cure rate was almost similar in HIV-positive (40.%) and HIV-negative RMR-TB patients (41.%). It was observed that 15.% of HIV-positive and 25.% of HIV-negative patients with RMR-TB failed treatment, even with the high rate of initial sputum culture conversion at the end of the intensive phase of treatment. The p-value shows no significant difference in the treatment outcomes in HIV-positive and HIV-negative patients with RMR-TB. Although it did suggest poor treatment outcomes, despite early sputum culture conversion.

5.10.3. Isoniazid mono-resistant TB patients

It was shown in Table 31, that the sputum culture conversion rate was higher in the first 6 months of treatment in both HIV-positive and HIV-negative HMR-TB patients.It was observed that 7.1% of HIV-positive and 28% of HIV-negative patients with HMR-TB failed treatment, even with the high rate of initial sputum culture conversion at the end of the intensive phase of treatment. The p-value -treatment outcomes HIV-negative patients with HMR-TB. This study is consistent with a study conducted in Taiwan during an 8-year period (2004- 2011). The authors documented worse treatment outcomes despite early sputum culture conversion in HMR-TB patients (Chien et al., 2015). It was revealed by the authors that 68.7% had poor treatment outcomes.

5.11. Impact of sputum culture reversion on the treatment outcomes

5.11.1. MDR-TB patients



It was observed in section 4.11.1 that 14 (6.1%) MDR-TB patients' (3 HIV-positive and 11 HIV-negative) sputum cultures reverted during the continuation phase of treatment, after initial sputum culture conversion at the intensive phase of treatment.Other investigators from the United States of America, Latvia, Estonia, Philippines, Russia and Peru that conducted a study during a 5-year period (2000-2004) documented a reversion rate of 23.7% in MDR-TB patients (Kurbatova et al., 2011). Janssen et al (2012), who conducted a study in Gauteng in South Africa during a 2 years period (2008-2009), documented a reversion rate of 11.6% (after 1 month), and 5.4% (after 2 months), after initial sputum culture conversion in 336 patients. Another investigator from Latvia who conducted a study during a 1-year period (between 1 January 2006 and 31 December 2006) documented an 11% reversion rate after initial sputum culture conversion in 167 MDR-TB patients (Holtz et al., 2006).

Of these 14 MDR-TB patients'whose sputum culture reverted after initial conversion, 11 failed treatment and only 3 were cured. The failure rate was high in MDR-TB patients who reverted after initial sputum culture conversion (79%), as compared to the cure rate (21%). This study's finding is inconstrast with a study conducted in Latvia by Holtz et al

(2006), who observed patients during a 1 year period (1 January 2006 to 31 December 2006). They reported an 11% (14)reversion rate and failure in only one patient, with the other patients having successful outcomes.

These patients in our cohort were discharged from hospital after initial sputum culture conversion at the end of the intensive phase of treatment, their sputum cultures reverted from a negative sputum cultures to positive during the continuation phase of treatment. These patients survived for long periods living in the community and are likely to contribute to community-based spread of DR-TB. It was also observed that during the continuation phase of the treatment there were fewer culture tests done on these groups of patients. This could suggest that adherence was a problem in these groups of patients.

5.11.2. Rifampicin mono-resistant-TB patients

It was observed that only 2 patients with RMR-TB reverted sputum cultures after initial sputum culture conversion at the end of the intensive phase of treatment. Of these 2 patients one failed treatment and the other patient's outcome was unknown.

5.11.3. Isoniazid mono-resistant -TB patients

No reversion was seen in this group of patients.

5.12. Could HIV infection influence the time to sputum culture conversion in patients infected with drug-resistant TB?

We were able to effectively establish and calculate the sputum culture conversion time in HIV–positive and HIV-negative patients with MDR-TB, RMR-TB and HMR-TB respectively by using the ICLIFETEST procedure.

5.12.1. Multidrug resistant TB patients

The median time to sputum culture conversion was similar inHIV–positive and HIV-negative patients with MDR-TB. Although no difference was found between the time to sputum culture conversion in HIV-positive and HIV-negative, patients with MDR-TB, Figure 1 show that HIV-positive patients with MDR-TB tend to have a worse survival

rate during MDR-TB treatment before experiencing clinical deterioration than HIV-negative patients with MDR-TB. As shown in Figure 1, the estimated survival probabilities are undetermined within the Turnbull intervals.

Our findings supported the views of Brust et al (2011) and Hafkin et al (2013),who found no significant differences between the time to sputum culture conversion in HIV positive and HIV-negative patients with MDR-TB at the end of the intensive phase of treatment. The only exception to this was with regard to survival time, indicating that the number of patients contributing to survival time was undetermined for the long-term treatment in MDR-TB (Fig 1). This demonstrates that HIV–positive patients with MDR-TB who survive after the intensive phase of treatment do appear to have worse survival rates as compared to MDR-TB patients without HIV infection (Figure 1). This shows that early sputum culture conversion (favourable microbiologic outcomes) do not predict equal favourable clinical recovery over the long term (continuation phase) of MDR-TB treatment.

This study confirms and extends the understanding of the influence of HIV-infection on the time to sputum culture conversion in MDR-TB patients observed in recent studies by Brust et al (2011) and Hafkin et al (2013), who only observed MDR-TB patients at the end of the intensive phase of treatment.

5.12.2. Rifampicin mono-resistant TB patients

HIV infection did not affect the time to sputum culture conversion in RMR-TB patients. Figure 2 shows that HIV-positive patients with RMR-TB tend to have a worst survival rate during DR-TB treatment before experiencing clinical deterioration than HIV-negative patients with RMR-TB. As shown in Figure 2, the estimated survival probabilities are undetermined within the Turnbull intervals. This shows that early sputum culture conversion (favourable microbiologic outcomes) do not predict equally favourable clinical recovery over the long term (continuation phase) of RMR-TB treatment.No recent study has investigated the influence of HIV infection on the time to sputum culture conversion in Rifampicin mono- resistant TB patients.

5.12.3. Isoniazid mono- resistant TB patients

Although no differences were seen in the time to sputum culture conversion by HIV status,HIV-positive patients with HMR-TBtend to survive longer during DR-TB treatment before experiencing clinical deterioration than HIV-negative Isoniazid mono-resistant TB patients as shown in Figure 3, although the estimated survival probabilities are undetermined within the Turnbull intervals.This shows that early sputum culture conversion (favourable microbiologic outcomes) do not predict equally favourable clinical recovery over the long term (continuation phase) of HMR-TB treatment.No recent study has investigated the influence of HIV infection on the time to sputum culture conversion in Isoniazid mono- resistant TB patients.

5.13. Could inappropriate (i.e. low and high) anti-TB drug dose influence the time to sputum culture conversion in drug-resistant TB patients?

5.13.1. Multidrug resistant TB patients

When inappropriate (i.e. low and high) anti-TB drug dose was correlated with the sputum culture conversion time in MDR-TB patients,it was revealed that inappropriate (i.e. low and high) anti-TB drug dosehas no influence on the time to sputum culture conversion in MDR-TB patients. Although no difference was found in the influence of inappropriate (i.e. low and high) anti-TB drug dose on the time to sputum culture conversion in MDR-TB patients, we may that inappropriate (i.e. low and high) anti-TB drug dose might be one of the factors influencing the time to sputum culture conversion. Figure 5 shows clearly that MDR-TB patients who receive any low anti-TB drug dose tend to have the survival before experiencing clinical deterioration, as compared to MDR-TB patients who did not receive any low anti-TB drug dose. As shown in Figure 5, the estimated survival probabilities are undetermined within the Turnbull intervals.

This suggests that the relatively low rate of treatment success in MDR-TB may be associated with low serum concentrations of anti-MDR-TB drugs (Lee et al., 2015). According to Lee et al (2015), such low anti-TB drug concentrations have been associated with malabsorption, alcohol use, age, sex, hyperalbuminemia, weight-adjusted dose, and drug formulation.

Figure 6reveals that MDR-TB patients who receive any high anti-TB drug dose MDR-TB patients who did not receive any high anti-TB drug dose. Although the estimated survival rate was undetermined due to the Turnbull interval.One might have expected that patients who received high anti-TB drug dose would have a more rapid time to sputum culture conversion than patients who received low anti-TB drug dose. Therapeutic drug monitoring (TDM) has been recommended by some clinicians as being particularly useful for more complicated patients, including those with more co-morbidities than ordinary patients responding to standard treatment (Lee et al., 2015). During the course of complicated MDR-TB treatment with second-line drugs, TDM allows the clinician to make an informed decision about poor drug absorption and to adjust the treatment accordingly in a timely manner (Lee et al., 2015). According to Lee et al (2015), TDM shortens the time to sputum culture conversion through adjusting drug dose and decreasing the adverse effects of high levels of anti-TB drugs.This is the first study to investigate the influence of inappropriate (i.e. low and high) anti-TB drug dose on the time to sputum culture conversion in MDR-TB patients.

5.13.2. Rifampicin mono-resistant TB patients

It was revealed in this study that inappropriate (i.e. low and high) anti-TB drug dose has no influence on the time to sputum culture conversion in RMR-TB patients. Although no difference was found in the influence of inappropriate (i.e. low and high) anti-TB drug dosage on the time to sputum culture conversion in RMR-TB patients, We may conclude that inappropriate (i.e. low and high) anti-TB drug dose might be one of the factors influencing the time to sputum culture conversion.

Figure 9 reveals that RMR-TB patients who receive any high anti-TB drug dose RMR-TB patients who did not receive any high anti-TB drug dose. However, the estimated survival rate was undetermined due to the Turnbull interval. One might expect that patients who received high anti- TB dose would convert faster than patients who received low anti-TB drug dose. This is the first study to investigate the influence of inappropriate (i.e. low and high) anti-TB drug dose on the time to sputum culture conversion in RMR-TB patients.

5.13.3. Isoniazid mono-resistant TB patients

It was shown in the previous section that HMR-TB patients did not receive any low anti-TB drug dose. Inappropriate (high) anti-TB drug dose has no influence on the time to sputum culture conversion in HMR-TB patients. Although no difference was found in the influence of inappropriate (high) anti-TB drug dose on the time to sputum culture conversion in HMR-TB patients,we may conclude that inappropriate (high) anti-TB drug dose might be one of the factors that influences the time to sputum culture conversion in HMR-TB.Figure 11 reveals that HMR-TB patients who receive any high anti-TB drug dose tend to have worse survival prospects than HMR-TB patients who did not receive any high anti-TB drug dose. However,the estimated survival rate was undetermined due to the Turnbull interval.One might expect that patients who received high anti- TB drug dose would convert sputum faster than patients who received low anti -TB drug dose.

Compliance rate may be another critical factor affecting the sputum conversion during the early period of treatment. Studies have shown that concomitant prescription of at least five anti-TB drugs and a relatively high incidence of secondary anti-TB drug–associated side effects can cause low compliance (Lee et al., 2015). Although no significant differences were found, it was observed in this study that suboptimal dosing could have an effect on the time to sputum culture conversion in these groups of patients. More studies are needed to investigate this.This is the first study to investigate the influence of inappropriate (low and high) anti-TB drug dose on the time to sputum culture conversion in HMR-TB patients.

5.14.To what extent do changes in immunological and virological profile influencetreatment outcomes in HIV-positive patients with drug resistant TB?

5.14.1. MDR-TB patients

HIV-infection is a microbiological factor that is dependent on CD4 count and viral load. HIV-positive patientshadimmunological and virological profiles, since out of 48 HIV-positive patients with available CD4 count data had a CD4 count cells/mm^3. And 6 HIV-positive patients with MDR-TB had viral load less than 40 copies/ml.

Decrease in CD4 count and viral load from baseline to the end of treatment with poor treatment outcomes were seen in 3 HIV-positive patients with MDR-TB.The 3 MDR-TB patients received ART after TB treatment. This study finding suggests that HIV-positive patients with MDR-TB who had a decrease in CD4 count and viral load from baseline,right through to the end of treatment, may have had undetected antiretroviral resistancebefore DR-TB treatment was initiated. In this study, we did not assess resistance to ARVs.However, we cannot rule out resistance of ARVs as one of the causes of poor DR-TB treatment outcomes in patients treated with ARVs. And this has been reported by similar previous studies (Satti et al., 2013; Andries et al., 2013).

Patients receiving concurrent DR-TB treatment and ART can experience clinical deterioration for a number of reasons other than ART failure. This includes severe side effects of treatment, treatment failure, new opportunistic infections and TB-associated immune reconstitution inflammatory syndrome (Brust et al., 2010). Satti et al (2013) shared their experience of six cases of antiretroviral drug-resistant TB patients with HIV co-infection in Lesotho. They reported that three patients died before or immediately after antiretroviral resistance was detected by genotyping, and the remaining three patients' culture converted within 2 months after being switched to effective antiretroviral therapy containing ritonavir-boosted lopinavir. These three patients were cured after 24 months of treatment and they showed dramatic immunological and virological improvement. The researchers propose that where HIV-drug resistance is suspected, switching the patients to an effective ART would improve outcomes. Although the exact causes of HIV-drug resistance are not well defined, they point out that

it is reasonable to suspect the prevalence and risk factors in patients co- infected with HIV and TB. They believe that HIV-drug resistance to anti-retroviral drugs may be related to poor clinical outcomes, but they agree that there is much more research needed in this field and encourage researchers in other parts of the world to pursue and investigate this.

Andries et al (2013) also agreed that HIV drug-resistance should be suspected in any patients with HIV-infection who fail to respond to therapy despite good adherence to treatment.

5.14.2. Rifampicin mono-resistant TB patients

Decrease in CD4 count and viral load from baseline right throughto the end of treatment was only seen in 2 HIV-positive patient with RMR-TB. Although the outcomes of the 2patients were one cured and the other defaulted treatment. In this study, we did not assess resistance to ARVs.However, we cannot rule out resistance of ARVs as one of the causes of poor DR-TB treatment outcomes in patients treated with ARVs. And this has been reported by similar previous studies (Satti et al., 2013; Andries et al., 2013).

5.14.3 Isoniazid mono-resistant-TB patients

There was no data with which to compare this group of HIV-positive patients.

5.15. Could antiretroviral duration before anti-TB treatment influence the treatment outcomes in HIV-positive patients with MDR-TB?

5.15.1. MDR-TB patients

The HIV-positive patients with MDR-TB with available ART data before anti-TB treatment (25) involved in this study had been on ART for216.5 days (IQR 18-1897). The duration of exposure is long enough to show an interaction between ARVs and anti-TB drugs, if any. Antiretroviral duration before TB treatment does not influence the

treatment outcomes in HIV-positive patients with MDR-TB. It was shown that there are no differences between the median duration of antiretroviral treatment in HIV-positive patients with MDR-TB in regard toboth those who were cured and failed. This study finding is consistent with a study conducted in South Africa that found no differences in the duration of ARV therapy on the treatment outcomes of HIV positive patients with MDR-TB (Mugabo et al., 2015).Antiretroviral therapy use before MDR-TB treatment was significantly associated with higher mortality in another study conducted in Gauteng South Africa (Umanah et al., 2015). The investigators reported these findings as surprising because they had not been reported anywhere before by other studies. It should be assumed that patients should have benefited from being on ARVs before MDR-TB treatment. The authors revealed that a greater percentage of patients who commenced ARVs before MDR-TB treatment initiation were severely underweight, had more extra-pulmonary TB, adverse events, and with modified regimen base on patients' history at baseline. They also reported that a lack of ART from poor adherence and treatment failure may have been responsible for the high mortality rate in HIV-positive patients who commenced ART before MDR-TB treatment.

5.16. Are there differences in the treatment outcomes among patients with MDR-TB, and mono-resistance TB?

It was revealed in the previous section that there are no differences among the cure rate in MDR-TB, RMR-TB and HMR-TB patients. In this study the cure rate was high in HMR-TB patients (56.4%), as compared to MDR-TB (42.6%) and RMR-TB patients (40.8%). The failure rate was high in MDR-TB patients (30.7%), as compared to RMR-TB (20.%) and HMR-TB (20.5%) patients. This study finding is consistent with a study conducted in South Africa by Mukinda et al (2012), who compared RMR-TB and HMR-TB patients, and demonstrated that RMR-TB was associated with failure. Other studies conducted in South Africa and the United States of America reported worse treatment outcomes inIsoniazid mono-resistant TB (Menzies et al., 2009; Jacobson et al., 2011).

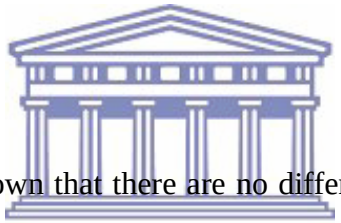
Another study conducted in Europe where Isoniazid mono-resistant TB, drug susceptible TB and MDR-TB were compared, the authorsreported Isoniazid mono-resistant TB and

MDR-TB to be associated with failure (Fox et al., 2011). A study conducted in Peru by Villegas et al (2016), who compared RMR-TB patients and HMR-TB patients, reported poor outcomes such as failure and death in HMR-TB patients and failure in RMR-TB patients.

The unknown outcome is high in RMR-TB patients (38.8%), as compared to MDR-TB (26.6%) and HMR-TB (23.%) patients. This suggests that RMR-TB patients were more likely to default treatment as compared to MDR-TB and HMR-TB patients. Mukinda et al. (2012) revealed that RMR-TB was linked to treatment default.

5.17. Could the replacement of ofloxacin by moxifloxacin influence the treatment outcomes in drug-resistant TB patients?

5.17.1. MDR-TB patients



From section 4.15.1, it was shown that there are no differences between the cure rate in MDR-TB patients receiving either ofloxacin or moxifloxacin-containing regimen. The cure rate was higher in MDR-TB patients who received moxifloxacin-containing regimen (46.9%), as compared to MDR-TB patients who received Ofloxacin-containing regimen (38.%). The failure rate was high in MDR-TB patients who received ofloxacin-containing regimen (32.%) as compared to MDR-TB patients who received moxifloxacin-containing regimen (26.5%). The unknown outcomewas almost similar in MDR-TB patients who received ofloxacin-containing regimen (28.%) and MDR-TB patients who received moxifloxacin-containing-regimen (26.5%).

Although there were no statistically significant differences in the treatment outcomes in MDR-TB patients that received either ofloxacin or moxifloxacin-containing regimen.There were a limited number of patients involved in the study. These study results show that, in spite of the limited number of patients, the replacement of ofloxacin by moxifloxacin did not improve the outcomes in MDR-TB patients.Studies have shown

that the current dosesof moxifloxacin (400 mg) and ofloxacin (800 mg) may thus be suboptimal for the treatment of drug-resistant tuberculosis if a pharmacodynamic target of $fAUC0_{-24}/MIC \geq 100$ correlates better with successful clinical outcomes (Chigutsa et al., 2012; Zvada et al., 2014). They propose susceptibility breakpoints of 0.125 mg/liter for 400 mg dose of moxifloxacin and 0.25 mg/liter for 800 mg ofloxacin. They believe that the current doses of 800 mg ofloxacin and 400 mg moxifloxacin may be related to poor clinical outcome, but agree that there is much more research needed in this field and they encourage researchers in other parts of the world to pursue and investigate this.

Our findings support the view of Chigutsa et al (2012) and Zvada et al (2014)which revealed that the current doses of 800 mg ofloxacin and 400 mg moxifloxacin used in the treatment of MDR-TB patients in South Africa is related to poor clinical outcomes. Zvada et al (2014) revealed that the currently used dose of moxifloxacin 400 mg is more efficacious than ofloxacin in the treatment of multidrug-resistant TB patients. They revealed that doubling the dose of moxifloxacin to 800 mg could achieve better outcomes in patients.

5.17.2. Rifampicin mono-resistant TB patients

From section 4.15.2, we see that the cure rate was higher in RMR-TB patients who received moxifloxacin-containing regimen (45.%), as compared to RMR-TB patients who receive ofloxacin-containing regimen (33.3%). The failure rate was high in RMR-TB patients who received ofloxacin-containing regimen (28.%) as compared to RMR-TB patients who received moxifloxacin-containing regimen (15.%). The unknown outcome was high in RMR-TB patients who received ofloxacin-containing regimen (38.1%), as compared to RMR-TB patients who received moxifloxacin-containing regimen (2%). Although no significant difference was observed between the treatment outcomes in RMR-TB patients that received either ofloxacin or moxifloxacin-containing regimen, from the result we could suggest that the replacement of ofloxacin by moxifloxacin tends to improve the outcomes in RMR-TB patients.However, a limited number of patients were involved in the study.

5.17.3. Isoniazid mono-resistant TB patients

As shown in section 4.15.3, the cure rate was high in HMR-TB patients who received ofloxacin-containing regimen (85.7%), as compared to HMR-TB patients who receive moxifloxacin-containing regimen (33.3%). The failure rate was worse in HMR-TB patients who received moxifloxacin-containing regimen (44.4%), as compared to HMR-TB patients who received ofloxacin-containing regimen (0%). The unknown was high in HMR-TB patients who received moxifloxacin-containing regimen (22.2%), as compared to HMR-TB patients who receive ofloxacin-containing regimen (14.%).Although there were no differences in the treatment outcomes in HMR-TB patients who received either ofloxacin or moxifloxacin-containing regimen, we could say that the replacement of ofloxacin by moxifloxacin did not improve the cure rate in all 39 HMR-TB patients. However, a small number of patients were involved in the study.

This suggests that the current moxifloxacin dose of 400 mg does not improve treatment outcomes in HMR-TB patients. Studies have shown that the current doses for moxifloxacin (400 mg) and ofloxacin (800 mg) may thus be suboptimal for the treatment of drug-resistant tuberculosis if a pharmacodynamic target of $fAUC0_{-24}/MIC \geq 100$ correlates better with successful clinical outcomes (Chigutsa et al., 2012; Zvada et al., 2014). Our findings support the view of Zvada et al (2014) whichrevealed that the current dose of 400 mg moxifloxacin used in the treatment of DR-TB patients in South Africa are related to poor clinical outcomes.

5.18. Could the fact of being infected with pulmonary TB, extrapulmonary TB, or co-infected with pulmonary TB and extrapulmonary TB affect the treatment outcomes in drug resistant TB patients?

5.18.1. MDR-TB patients.

In the previous chapter, we have demonstrated that there are no significant differences among the treatment outcomes in MDR-TB patients infected with pulmonary TB, extrapulmonary TB and co-infected with pulmonary TB and extrapulmonary respectively. Due to the limited number of patients with extrapulmonary TB and patients co-infected with pulmonary TB and extrapulmonary TB, we cannot definitely conclude that indeed no significant differences exist in the treatment outcomes among these groups of patients.

The cure rate was poor in MDR-TB patients infected with extrapulmonary (38.46%) and MDR-TB patients infected with pulmonary TB (42.%), as compared to MDR-TB patients co-infected with pulmonary TB and extrapulmonary TB (75%). The failure rate was high in MDR-TB patients infected with pulmonary TB (31.7%), as compared to MDR-TB patients infected with extrapulmonary TB (23.%). The unknown outcome was high in MDR-TB infected with extrapulmonary TB (38.%), as compared to MDR-TB patients infected with pulmonary TB (2%) and MDR-TB patients co-infected with pulmonary TB and extrapulmonary TB (25%). In this study, it was observed that MDR-TB patients infected with pulmonary TB were more likely to fail treatment, as compared to MDR-TB patients infected with extrapulmonary TB, and patients co-infected with pulmonary TB and extrapulmonary TB. This study finding are consistent with studies conducted in South Africa and the United States of America that reported poor treatment outcomes in MDR-TB patients infected with extrapulmonary TB (Gandhi et al., 2012; Kurbatova et al., 2012).

5.18.2. Rifampicin mono-resistant-TB patients

The cure rate was poor in RMR-TB patients infected with extrapulmonary TB (0%) as compared to RMR-TB patients infected with pulmonary TB (41.8%). Although the number of patients involved was few and there were a limited number of patients involved in the study.

The failure rate was highin RMR-TB patients infected with extrapulmonary TB (50%), as compared to RMR-TB patients infected with pulmonary TB (19.%). The unknown

outcome was high in RMR-TB patients infected with extrapulmonary TB (50%), as compared to RMR-TB patients infected with pulmonary TB (38.8%). There were no data to compare the outcomes in RMR-TB patients co-infected with pulmonary TB and extrapulmonary TB. This suggests that RMR-TB patients infected with extrapulmonary TB tend to have worse treatment outcomes as compared to RMR-TB patients infected with pulmonary TB. Studies have revealed an association between RMR-TB and extrapulmonary TB (Sandman et al., 1999; Vernon et al., 1999).But no recent studies have looked at the influence of DR-TB localization on the treatment outcomes in RMR-TB.

5.18.3. Isoniazid mono-resistant TB patients

The cure rate was lower in Isoniazid mono-resistant TB (HMR-TB) patients infected with pulmonary TB (54.%) as compared to HMR-TB patients infected with extrapulmonary TB (100%). The failure rate was higher in HMR-TB patients infected with pulmonary TB (21.6%) as compared to HMR-TB patients infected with extrapulmonary TB (0%). The unknown outcome was high in HMR-TB patients infected with pulmonary TB (24.3%) as compared to HMR-TB patients with extrapulmonary TB (0%). There were insufficient data to compare the outcomes in HMR-TB patients co-infected with pulmonary TB and extrapulmonary TB. This suggests that HMR-TB patients infected with extrapulmonary TB tend to have better treatment outcomes as compared to HMR-TB patients with pulmonary TB. But we had only a few patients infected with extrapulmonary TB.

5.19. Limitations of the study

This was a retrospective study so data collection was based on the available clinical records and the data available in the drugresistant tuberculosis register. There was no balance in the DR-TB localization dataamong the drug resistant TB group of patients. Mostpatients were infected with pulmonary TB, few patients were infected with extrapulmonary TBvery few patients were infected with both pulmonary and extrapulmonary TB. It was thus difficult to compare the cure rates in this group of

patients. Our sample size was too small for us to evaluate some well-known types of extrapulmonary TB (e.g., pleural, cutaneous, pericardial, lymph nodes, meninges, peritoneal cavityand intra-abdominal organs). In addition, there was no balance in the drug resistance TB data. Few patients had Isoniazid mono-resistant TB, and thus it might be difficult to conclude the influence of drug resistance on the treatment outcomes in patients.Limited CD4 counts and viral load data prevented assessment of whether the changes in CD4 count and viral load influenced the treatment outcomes**.**

Notably, the scope of this study did not extend to explore the influence of genotypic strains of *Mycobacterium tuberculosis* on MDR-TB, RMR-TB and HMR-TB clinical outcomes, which is an important microbiological factor to be considered.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In conclusion, we were able to achieve most of the objectives set out for this study. This was successfully achieved by using the ICLIFETEST procedure for the determination of time to sputum clearance in both groups of patients. We therefore accept the null hypotheses in our first and second experimental hypotheses.

We found no evidence of a significant difference between the two population groups with regard to time to sputum culture conversion, the exception to this being with regard to survival time, which was not defined, indicating that MDR-TB and RMR-TB patients with HIV infection who survived during DR-TB treatment had worse survival prospects than HIV-negative MDR-TB, and RMR-TB patients.

HIV-positive patients with Isoniazid mono-resistant TB who survived during DR-TB treatment tend to survive longer before experiencing clinical deterioration than HIV-negative patients with HMR-TB.

The ICLIFETEST procedure was also used to correlate the effect of inappropriate anti-TB drug dose on the sputum culture conversion time in MDR-TB, RMR-TB and HMR-TB patients. We found no evidence of a significant difference between the two population groups with regard to the effect of inappropriate anti-TB drug dose on the time to sputum culture conversion in MDR-TB, RMR-TB and HMR-TB patients, the exception to this being with regard to survival time which was not defined,. We therefore fail to reject our experimental hypotheses and accept the null hypotheses in these cases.

We found that treatment outcomes were statistically significantly worse for HIV-positive patients with MDR-TB as compared to HIV- negative patients despite early sputum culture conversion. We also found that treatment outcomes were statistically significantly worst for HIV-negative patients with HMR-TB as compared to HIV –positive patients with HMR-TB despite early sputum culture conversion. We therefore accept our experimental hypotheses. We

found no evidence of a significant difference between the other microbiological parameters studied with regard to MDR-TB, RMR-TB and HMR-TB treatment outcomes. We therefore fail to reject our experimental hypotheses and accept the null hypotheses in these cases.

Our research was limited by an unbalanced distribution in Isoniazid mono-resistant TB cases, extrapulmonary TB cases, and ART history, as well as the inability to assess whether changes in CD4 counts and viral load affects the treatment outcomes in DR-TB patients.

This study shows that early (microbiological outcome) sputum culture conversion does not suggest early clinical recovery. This is suggestive of other factors e.g pharmacokinetic, drug-drug interactions, such asARVs and anti-TB drugs, drug-food interactions, drug-disease interactions that influence the treatment outcomes in drug-resistant TB patients.

Therefore with regard to the result obtained in this study, we can conclude that the objectives of the present study were achieved:

- The sputum culture conversion time in DR-TB patients and DR-TB co-infected with HIV was described.
- HIV infection does not have any influence on the time to sputum culture conversion in DR-TB patients.
- Inappropriate (i.e low and high) anti-TB drug dose does not have any influence on the time to sputum culture conversion in DR-TB patients.
- Antiretroviral duration before TB treatment does not have any influence on MDR-TB outcomes.
- There are no differences in the treatment outcomes between MDR-TB and mono-resistant–TB cases.
- The replacement of ofloxacin by moxifloxacin does not improve the treatment outcomes in DR-TB patients.
- The fact of being infected with extrapulmonary TB does not influence the treatment outcomes in DR-TB patients.

This objective was not achieved due to limited data

- Changes in CD4 count and viral load from baseline to the end of treatment do not influence the treatment outcomes in HIV-positive patients with DR-TB.

6.2 Recommendations

Based on the above-mentioned limitations, the following should be considered for future studies:

- Changes in CD4 count at different intervals should be determined, because it helps to check the relationship between HIV infection and treatment outcomes i.e. HIV drug resistance, which will aid to know if HIV-positive patients need to switch to other ARVs.
- Studies are neededwith a higher number of HIV-positive patients with drug-resistant TB, with available immunological and virological data to give a better understanding of the influence of the immunological and virological profile on DR-TB treatment outcomes.
- Sputum culture reversion should be studied and the real causes or risk factor for culture reversion should be studied.
- Further characterization of these patients with delayed conversion is needed to determine potential causes of persistent culture positivity. For patients who do not convert in the first six months of treatment.
- Studies are needed with higher number of patients with Rifampicin mono-resistant TB and Isoniazid mono-resistant TB to confirm and extend the understanding of the influence of HIV- infection on the time to sputum culture conversion.

- Studies focusing on inappropriate (low and high) anti-TB drug dose to look at patient's body weight for the 24 months of treatment and the dose of anti-TB drugs patients were receiving. These studies would also have to find out the reason why patients were receiving inappropriate anti-TB dose, to check if they had other co-morbidities or if thedrug dose was adjusted by the clinicians and the reasons.
- More studies are needed to investigate the influence of ART before anti-TB treatment on MDR-TB treatment outcomes.
- More studies are needed to look at the influence of DR-TB localization on MDR-TB, RMR-TB, and HMR-TB treatment outcomes.
- Influence of HIV infection on the time to sputum culture conversion in RMR-TB and HMR-TB patients should be studied.

- Larger number of extrapulmonary TB patients should be studied (e.g., pleural, cutaneous, pericardial, lymph nodes, meninges, peritoneal cavity, and intra-abdominal organs) and their influence on the treatment outcomes in Rifampicin mono-resistant TB, Isoniazid mono-resistant TB and MDR-TB patients.
- One microbiological factor that was not assessed in this study is the genotypic strain of *Mycobacterium tuberculosis* on the treatment outcomes in MDR-TB, RMR-TB, and HMR-TB patients. This is an important microbiological parameter that should be considered in further studies.

- There is much more research needed in the area of microbiological parameters in MDR-TB, RMR-TB and HMR-TB patients, especially in South Africa. Even greater is the need to explore these microbiological parameters in the HIV positive population, as these patients make up a significant proportion of the DR-TB patient population in South Africa. Further investigation with a high number of patients is required in order to establish if these patients are being exposed to inappropriate (i.e low and high) anti-TB drug dose, and whether or not this has an impact on DR-TB treatment outcomes.

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