

**CLINICAL CHARACTERISTICS AND TREATMENT
OUTCOMES OF MULTI-DRUG RESISTANT TUBERCULOSIS
PATIENTS ATTENDING A HOSPITAL IN BUFFALO CITY
METROPOLITAN MUNICIPALITY, EASTERN CAPE**

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A mini-thesis submitted in partial fulfilment of the requirements for the
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KEY WORDS

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Human Immunodeficiency Virus (HIV)

Co-morbidities

Adherence to treatment

Pill burden

Adverse effects/ events

Clinical characteristics

Treatment outcomes

South Africa



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ABSTRACT

Background: The presence of highly effective medicines has made very little impact in reducing deaths as a result of tuberculosis (TB), a curable condition but when managed inappropriately, may result in Drug Resistant TB. TB accounts for about one in four deaths that occur in HIV positive people and HIV has been found to be a risk factor for complex unfavorable outcomes in MDR TB patients and a very strong predictor for death and default. The relationship between diabetes and TB has also been explored, with some authors identifying diabetes as a risk factor for TB, and with related poor clinical outcomes in both conditions when they co-exist. Exploring the clinical characteristics and treatment outcomes of MDR TB patients in the presence of these risk factors could present an opportunity to provide better care through increased case-detection activities, improved clinical management and better access to care for all these conditions. The aim of the study was to describe the clinical characteristics and treatment outcomes of MDR TB patients initiated on treatment at Nkqubela and Fort Grey Hospitals.

Methodology: This was a retrospective chart review of MDR TB patients who were initiated on treatment at Nkqubela and Fort Grey Hospitals between January 2013 and June 2014. The study population included all MDR TB adult patients who met the inclusion criteria. Of the 928 patients registered on EDR.web database during this period, 332 were included in the final analysis. A customized data collection tool was used to collect patient data using EDR.web database and patient folders. STATA version 15 was used for data cleaning, management and statistical analysis. Descriptive analyses were used to summarize data, measure central tendency and dispersion and measures of association and their 95% confidence intervals were used to measure strength of association. Chi-square and t-tests were used to test for statistical significance at univariate level and multiple regression models used to determine associations between factors and treatment failure.

Ethics: Ethical approval and permission to conduct the study were obtained from the relevant authorities. Patient confidentiality was maintained throughout the study.

Results: A total of 332 patients were included in the final analysis, comprising 57.5% (n=191) men and 42.5% (n=141) women, with a median age of 39.4 years; 75.9% (n=252) were unemployed and 60.2% (n=200) lived in rural areas. Two hundred and forty five (245) (73.8%)

patients were HIV positive and 89% were reported to be on ART. Diabetes was rare, with only 4.2% (n=14) of the sample reported as diabetic. Overall, 28.0% (n=93) of the patients were cured, 6.6% (n=22) completed treatment; 44.3% (n=147) died; 11.1% (n=37) defaulted treatment; 4.8% (n=16) failed treatment and 3% (n=10) were transferred out. Site of current TB, a positive HIV status and taking more than five drugs were statistically significantly associated with death, with reported aOR of 2.91(1.03 – 8.19; p = 0.043); 1.88 (1.07 – 3.31; p = 0.027) and 3.21 (1.04 – 10.14; p = 0.046), respectively.

Conclusion: These findings reflect a struggling MDR TB control program. More work still needs to be done and more efforts made in reducing the spread of MDR TB in rural areas and amongst the poor. Though diabetes was rare in this study, a further exploration of its impact and that of other co-morbidities on MDRTB management needs to be considered.



DECLARATION

I declare that **Clinical characteristics and treatment of outcomes of Multi-Drug Resistant Tuberculosis patients attending a hospital in Buffalo City Metropolitan Municipality, Eastern Cape**, is my own work, that it has not been submitted before for any degree or examination in any University or College, and that all the sources I have quoted or used have been indicated and acknowledged as complete references.

Olwethu Jikijela

January 2018

Signed:



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DEDICATION

This work would not have been possible without God, Who was, and is, and is to come. Lord, I thank You.

To my friends and family, thank you for standing in the gap when I appeared to be greatly consumed by this work.

To my husband Mzu, thank you for bearing with me, for believing in me and so understanding through it all. You have been my pillar of strength and I doubt I would have made it this far without your love, encouragement and support. Enkosi Gqugqugu!

And my kids, Onako, Uyanda and Hlumelo, you guys are just amazing! I just thank God for you and your father. You've just been such wonderful companions throughout this journey, thank you Makhomazi Amahle.



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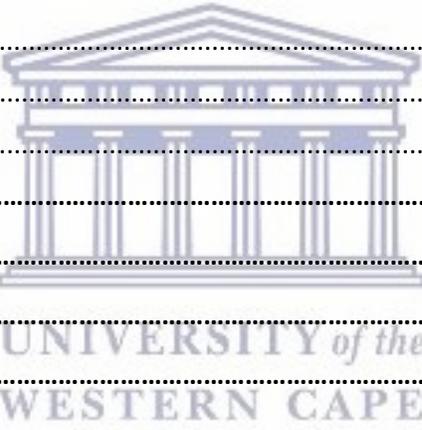
To Tonya, thank you for your assistance with data management, cleaning, statistical analysis and the discussion. Your contribution to this minithesis is invaluable. Words cannot describe how grateful I am that God put you in my path. Giving up your 3 days of family and work life so that you could be at the writing retreat assisting me is beyond anything that I have ever imagined, and for that, thank you. The knowledge you imparted in me will forever be held dear and it is one of the reasons why I don't feel so intimidated by research anymore. Thank you.

SUCCEED thank you for making a difference not only in my life but to the community of Butterworth hospital at large. Your financial contribution and mentorship you provided made it possible for this project to be carried out. Please continue the great work and continue to inspire us to dream beyond our current circumstances.

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ACRONYMS

AE – Adverse Event

BCMM – Buffalo City Metropolitan Municipality

DM – Diabetes Mellitus

DR TB – Drug Resistant Tuberculosis

DOTS - Directly Observed Treatment Strategy

EDR.web – South African Electronic Drug-Resistant Tuberculosis Register

HAART – Highly Active Anti-retroviral Treatment

HIV – Human Immunodeficiency Virus

INH – Isoniazid

MDR TB – Multi-Drug Resistant Tuberculosis

MTB – Mycobacterium tuberculosis

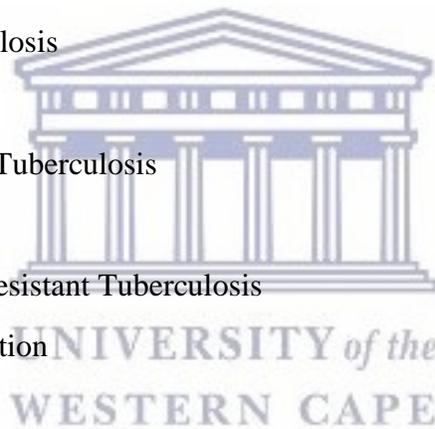
PTB – Pulmonary Tuberculosis

RR TB – Rifampicin Resistant Tuberculosis

TB – Tuberculosis

XDR TB – Extensively Drug Resistant Tuberculosis

WHO – World Health Organisation



DEFINITION OF KEY CONCEPTS AND TERMS

Adjunct treatment – an additional treatment used to increase the efficacy or safety of a primary treatment.

Adverse effect – an undesired harmful effect resulting from a medication or other intervention such as surgery, may be termed a "side effect", when judged to be secondary to a main or therapeutic effect.

CD4 count – a laboratory test that measures the number of CD4 T lymphocytes (CD4 cells) in a sample of blood, an important indicator of immune function and the strongest predictor of disease progression in HIV positive individuals.

Co-morbidity – presence of one or more additional diseases or disorders co-occurring with a primary disease or disorder.

Decentralization – transfer of authority and patient management from the specialised TB hospital onto local authority, i.e., clinics, community health centres and district hospitals.

DR TB – is a disease caused by *M. tuberculosis* strains resistant to one or more anti-TB drugs.

Extra-pulmonary TB – TB in other organs other than the lungs.

HbA1c (Glycated Haemoglobin) – a haemoglobin that is measured primarily to identify the three-month average plasma glucose concentration.

MDR TB – TB disease where there is in vitro resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs.

Pill burden – the number of tablets, capsule or other dosage forms that a person takes on a regular basis.

XDR TB – MDR TB plus resistance to at least fluoroquinolones and/or the second-line injectable drug.

CHAPTER 1: INTRODUCTION

Tuberculosis (TB), a curable condition, remains a great concern in today's healthcare system. The presence of highly effective drugs has made very little impact in reducing deaths as a result of TB although the World Health Organisation (WHO) states that effective diagnosis and treatment of TB saved an estimated 53 million lives between 2000 and 2016 (WHO, 2017). TB can remain dormant in the body for many years, with a lifelong risk of reactivation. This reactivation is a high risk factor for disease development especially in immune compromised individuals such as those with Human Immunodeficiency Virus (HIV) infection or diabetes (Koul et al., 2011). Globally, it is estimated that 10.4 million people were infected with TB in 2016, 10% of those cases were HIV positive, with the Africa region accounting for 74% of those HIV positive cases (WHO, 2017). The treatment success rate for people newly diagnosed with TB was estimated at 83% in 2016 and in that same year TB was listed as the ninth leading cause of death in the world (WHO, 2017) and it was amongst the top four causes of death in South Africa in 2013, as highlighted in the South African Department of Health Strategy 2014/15 to 2018/19 (SADoH, 2014).

Poor management of TB results in Multi-Drug Resistant Tuberculosis (MDR TB). MDR TB refers to the resistance of *Mycobacterium tuberculosis* (MTB) to both rifampicin and isoniazid, which are two of the four drugs or active ingredients used as first line treatment for TB, both in the intensive and continuation phases. The WHO estimated that in 2016, 4.1% of new TB cases and 19% of previously treated cases had MDR/Rifampicin Resistant (RR) TB, and this translates to 490 000 people infected with MDR TB and 110 000 infected with RR TB, globally (WHO, 2017). In 2016, the WHO estimated that only 22% of the estimated incidence of people with MDR/RR TB were started on treatment. The Global TB Report (WHO, 2017), reported that only 54% of the MDR TB or RR TB patients who started treatment in 2014 were successfully treated; 16% died; 8% failed treatment, 15% were lost to follow up and 7% were not evaluated or had no outcome information.

In South Africa in 2014, there were 325 498 patients on TB treatment and only 77.2% were treated successfully; with the Eastern Cape reporting a treatment success rate of 76.2% and 72.2% cure rate during that period. During that period, TB remained the leading cause of death

in the country, accounting for 8.3% of deaths in the country and the Eastern Cape contributed 9% to those deaths in that year (Stats SA, 2015).

South Africa (SA) remains in the WHO's top 30 high burden countries for MDR TB as revised in 2016 (WHO, 2017). According to the WHO (2017), SA had an estimated incidence of 438000 active TB cases in 2016, estimating that about 0.8% of the population develops active TB each year and 59% of those are HIV positive; with 88% on ART. The TB cure rate increased from 61.6% in 2006 to 81% in 2015, but this was still slightly lower than the 2018/2019 target of >85% success rate for new TB treatment cases. The low TB cure rate is said to be worsened by poor adherence to drug treatment, late initiation to treatment and/or loss to follow up and it probably explains the emergence of drug resistant TB in the country, a result of an "expanded pool of infection" and resistance to first line TB treatment (WHO, 2016; SAdoH, 2014).

Drug resistant TB emerged in the 1980's in South Africa but was not thought to be a major problem, with Extensively Drug-Resistant TB (XDR TB) (defined as MDR TB plus resistance to at least fluoroquinolones and/or the second-line injectable drug) prevalent in the Western Cape as early as 1992 (Schaaf et. al, 1996; Weyer et. al, 1995; Symons et. al, 2011). In a national survey conducted in 2001-2002, the Eastern Cape had more than 10% MTB strains that were resistant to at least one drug. Around 2012, cases of MDR and XDR TB continued to increase, with 15419 and 1596 patients, respectively (Churchyard et. al, 2014). For those adults diagnosed in 2012, the treatment success rate for MDR and XDR TB patients remained low, at 42% and 18% respectively. In 2014, the WHO estimates that South Africa had 18734 laboratory confirmed Drug Resistant TB cases, with a 49% treatment success rate.

The treatment of MDR TB involves a cocktail of medicines, approved for use in second line TB treatment, with the regimen based on the history of drugs taken by the patient. The period of treatment is up to 24 months, that is, six months of intensive phase, as in- or out-patients, and 18 months of the continuation phase, as outpatients, depending on the date of seroconversion. For the first six months, patients are required to take five different drugs, and thereafter four different drugs in the 18 month long intensive phase. In practice this means that during the intensive phase regimen, patients take between eight and 14 tablets per day, depending on their weight, in addition to an injection, which has to be taken for the first four months after the treatment

conversion date. These drugs are quite expensive, with some studies estimating up to a 100 fold higher price than first line TB treatment (Umanah et al, 2014; White & Moore-Gillon, 2000).

New drug developments have, however, led to an accelerated seroconversion but these new regimens are not yet available to all patients, mainly due to cost. The introduction of bedaquiline in 2015 into the already existing regimens of MDR TB treatment was meant to strengthen the already existing regimens, especially for those patients resistant to or unable to tolerate fluoroquinolones and the second line injectable drugs, which are the mainstay of the MDR TB treatment, and thus increase treatment success rate in the country. Bedaquiline is said to reduce or accelerate sputum conversion by up to 2.5 months, compared to the current standard of care which requires up to 4.2 months and its use could reduce the need for second line injectable drugs which are associated with irreversible toxicity (WHO, 2013; Achar et al., 2017; Diacon et al. 2012).

As stated in the National Guidelines for TB management, factors that influence treatment outcomes in TB patients include socio-economic factors; patient related factors; health system factors and therapy related factors. Delayed initiation of treatment; inadequate treatment prescribed or dispensed, inadequate bed capacity, poor infection control measures in hospitals and poor adherence to treatment are also challenges to TB management. The clinical characteristics and treatment outcomes of MDR TB patients in the presence of risk factors like the presence of HIV; diabetes mellitus (DM); other co-morbidities; drinking; and the presence of a support system once the patient is discharged from the hospital needs to be explored. Thus, the aim of this study was to describe the clinical characteristics and treatment outcomes of MDR TB patients attending a hospital in the Eastern Cape, South Africa. Successful treatment of MDR TB in South Africa would mean a reduced incidence of XDR TB, which has proven to be very difficult to treat and has contributed quite significantly to the challenges in global TB control (WHO, 2016). An improved global TB control “will require an improved prevention of primary MDR TB including a better understanding of the relationship between diabetes and risk of MDR TB” (Salindri D, et al, 2016).

Research Problem

South Africa is facing a quadruple burden of disease, with non-communicable diseases (NCDs) contributing at least 33% to that burden (Bradshaw et al., 2000; SAdoH, 2014). The NCD

epidemic in SA is an even greater burden because it is occurring concurrently with an “ageing HIV-positive” population (Hofman, 2014) and added to that is the increase in drug resistant TB. Of note is the relationship between TB and diabetes with evidence showing that the presence of both diseases in one patient leads to poor clinical outcomes (ReyPineda, G, 2014). In addition to the relationship between TB and diabetes, TB is one of the most common opportunistic infections in HIV positive patients. HIV has been associated with increasing MDR TB prevalence among patients with TB and has been associated with many MDR TB outbreaks (Wells et al. 2007).

The average treatment regimen for a patient with MDR TB is up to five different drugs, with one patient taking up to 14 tablets plus an injection in the initiation phase, this number is greatly increased if a co-morbidity exists. This increased pill burden could have an impact on the clinical and treatment outcomes of these patients (Biruk et al. 2016).

Thus, a study to compare the clinical characteristics and treatment outcomes of those patients with MDR TB only; MDR TB with diabetes and/or HIV would assist in highlighting some of the successes in the different treatment programmes, and possibly assist in better management of these conditions in the future. Already, the first line treatment for HIV management is a fixed dose combination, thus reducing the pill burden by up to three or four tablets per day for a patient on first line treatment for HIV. So, does this lead to better treatment outcomes compared to those that are taking multiple tablets for diabetes management? If better, what lessons can we learn from HIV management in managing MDR TB in the presence of comorbidities?

Study significance

Understanding the management of MDR TB in the presence of co-morbidities could lead to improved treatment outcomes and could bring South Africa closer to the realization of the 90-90-90 goal, a “global strategy and target for TB prevention, care and control after 2015” and the realization of the National Development Plan 2030 vision, which seeks to “progressively improve TB prevention and cure and reduce prevalence of NCD’s” amongst other goals (WHO, 2017; National Planning Commission, 2011).

The WHO’s End TB strategy 2016-2035 (WHO, 2017), aimed at ending the global TB epidemic, was adopted in 2014 by the World Health Assembly. The main targets stated are to reduce TB

deaths by 95% and decrease new cases by 90% between 2015 and 2035. The strategy highlights the need to provide prompt treatment to 90% of all people with TB and providing prophylaxis to 90% of those who need it. It also highlights the need to reach 90% of key populations and achieve at least 90% treatment success for all people diagnosed with TB. The strategy also notes the need for a collaboration between TB and HIV activities, and the importance of managing co-morbidities when managing TB. The need for intensive research and innovation, leading to the “discovery, development and rapid uptake of new tools, interventions and strategies” and this research could also assist in optimizing the implementation and impact and promote innovation.

South Africa is currently decentralizing MDR TB management, encouraging and mandating Primary Health Care (PHC) facilities to initiate and manage patients with Drug Resistant (DR) TB thus allowing patients’ services closer to their places of residence and also affording them integrated services at PHC. Thus this study will give a general overview of the kinds of patients that are seen at these facilities, best ways to manage them and also to identify what the risk factors are for poor outcomes in this population. It will also identify which characteristics are associated with successful treatment outcomes so that programmes can identify those patients at risk for poor outcomes and formulate strategies in order to improve those poor outcomes.

Diabetes mellitus is contributing to increased TB burden and current evidence suggests that DM affects the disease presentation and treatment outcomes in drug susceptible TB patients but literature on the effect of diabetes on MDR TB is very limited or almost non-existent thus this study will seek to explore this further (Workneh et al. 2016; Dooley & Chaisson 2009; Sen et al. 2009).

Setting

The Eastern Cape is the third most populous province in South Africa, with a recorded 1.8 million households in 2016. Three quarters of the households have access to piped water, 85.4% have access to electricity and 52% have access to a flush or chemical toilet. The province was reportedly said to have a 12.7% poverty headcount in 2016, which was a decrease compared to a national census that was conducted in 2011, except in Chris Hani where the poverty headcount increased from 15.6% in 2011 to 16.4% in 2016 (DHB, 2017).

The research was carried out at Nkqubela Hospital, a specialised TB hospital, based in Mdantsane, in the Buffalo City Metropolitan Municipality (BCMM) region of the Eastern Cape.

Nkqubela Hospital is a referral hospital and has decentralized sites in six municipalities of the Eastern Cape, BCMM, OR Tambo, Amathole, Alfred Nzo, Chris Hani, and Joe Gqabi municipalities. These municipalities have a total of population of 1.4 million, accounting for 78% of the total population in the province and are mostly rural with a travelling distance of up to 500km or more from Nkqubela Hospital. Patients are admitted through referrals by other facilities, ranging from level one facilities (clinics) up to tertiary institutions.

In 2016 Nkqubela hospital was merged with Fort Grey TB hospital, another specialised TB hospital located within 30km of Nkqubela. These two hospitals were working independently of each other prior to the merger but could refer patients to each other during that time. Since the merger, they have been functioning as one unit, in the same location. For the period under review, the two hospitals worked as independent units thus the files reviewed belonged to patients from both hospitals, as the sample size would have been too small if either one of the hospitals was left out. Also the reason for including both hospitals is that currently, they are considered as one.

The current merged facility is a 320 bedded facility, specialising in MDR, XDR and drug susceptible TB, with a 70% bed occupancy/ utilization rate. Management of patients include in- and out-patients, with about 20 decentralised sites and a number of satellite sites within the province. MDR TB patients with sputum smear positive results are hospitalised in this facility until they have produced two negative sputum smears consecutively, however, patients presenting with smear negative, TB culture positive results are initiated on MDR-TB treatment in the community as per the 2013 National TB guidelines.

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction

This literature discusses the socio-demographic and clinical characteristics associated with TB, the role of HIV in TB management, presence of diabetes and other co-morbidities and the effect of pill burden on MDR TB management.

2.2. Socio-demographic characteristics associated with TB

Socio-demographic characteristics influence detection and successful treatment and have a great impact on successful TB programmes (Hudelson, 1996). The need to earn, homelessness or substandard housing conditions, alcoholism, access to treatment, available work or unemployment, monetary resources, access to food, living with TB contacts and poor experience with previous TB treatment were reported to be significantly associated with increased risk for TB and treatment default and were reportedly associated with high risk of TB transmission (Holtz et al. 2006; Franke et al. 2008; Coker et al. 2006). Healthcare workers also identified family migration as a contributing factor to MDRTB treatment default and a low education level, amongst other factors, was identified as a predictor for death after defaulting MDRTB treatment (Franke et al., 2008).

Franke et al (2008) reported that women were more likely to die at a higher rate than men. Gender differentials have been explored in other studies as well, with some studies concurring that TB impacts women more than men possibly because women are usually more poor and most disadvantaged in the households and they are at greater risk of HIV infection (Hudelson, 1996). However, a study by Goble et al. (1993) stated that the male gender was significantly associated with unfavorable treatment outcomes though the authors could not establish the reason for the association.

In a study conducted by Gebrezgabiher et al. (2016) in Ethiopia to determine the treatment outcome of TB patients and identify factors associated with unsuccessful outcomes, the authors reported that the treatment success was similar in males and females though more than two thirds of the sample was males. In the same study, the authors found that the rate of unsuccessful treatment was higher for patients living in rural areas compared to those who lived in urban areas. Other research from Ethiopia by Ramos et al. (2008) suggests that the differences found

between the urban and rural populations in treatment outcomes could be due to lower awareness about TB and the long distances from home to treatment centres in the rural population.

2.3. Clinical characteristics associated with TB

A successful first course of TB treatment is important, with patients who had previously defaulted TB treatment at increased risk of default and death (Lalor et al., 2013). The use of illicit drugs e.g. marijuana, mandrax, etc., during the treatment period and having an - unsatisfactory opinion about the attitude of the health workers were identified as risk factor for defaulting MDR TB treatment (Holtz et al. 2006). Some studies have also reported a strong association of number of drugs that the patient is resistant to, as a risk factor for treatment failure but not for death or default, with the KZN study reporting that nearly 25% of the patients in the study were resistant to more than 5 TB drugs (Brust et al., 2010; Meressa et al., 2015). In a survey conducted in 2001-2002, the Eastern Cape had more than 10% MTB strains that were resistant to atleast one drug (WHO, 2004).

In a study conducted in Ethiopia by Meressa et al. (2015), the treatment success rate for MDR TB was fairly high, with 64.7% of the patients cured; 13.9% having completed treatment; 5.9% lost to follow up and 13.9% of the patients died. This is higher than the 45% cure achievement or treatment completion reported by Brust et al. (2010) in SA. Factors associated with death were largely related to severity of disease at initiation of treatment (Lalor et al. 2013).

Adherence to treatment, the pill burden, presence of co-morbidities e.g. diabetes and HIV/AIDS, etc. and experiencing adverse effects (AEs) from either the disease or the treatment has been associated with unfavourable treatment outcomes, with Hudelson (1996) stating poor compliance to treatment is the most important cause of treatment failure in TB programmes.

2.4. Principles of MDR TB treatment

2.4.1. Adherence to treatment and pill burden

Adherence to treatment, especially during the intensive phase of treatment, is a critical factor in the management of MDR TB (Nathanson et al., 2004; SA National TB Guidelines, 2013). It has been associated with high TB cure rates. Though the gold standard for MDR TB management, post admission, should be DOTS, a strategy that was developed to enhance patient adherence,

reduce treatment interruption and improve treatment success rates, however, this is not always possible because of limited resources.

Factors that affect adherence include: dosing frequency; pill burden and side effects; patient-healthcare provider relationship; and the system of care (Chesney, 2000). Adherence has also been thought to be more difficult in MDR TB patients because of the prolonged duration of treatment and the associated toxicities of second-line medicines (SA National TB Guidelines, 2013). Age has also been associated with adherence to treatment, with Umanah et.al (2015) reporting that older adults adhere to treatment better compared to younger adults. Adherence strategies that can be employed in the management of MDR TB include monthly home visits, monthly patient visits to the treatment initiation sites, and identification of a patient supporter to assist with DOT, psychosocial support, provision of monthly food baskets and social support for the most destitute patients (Meressa et al., 2015). The success of this strategies is noted in some studies, with Calver et al. (2010) reporting an observed adherence of 95% to 98% when adherence was monitored by observing the patient receive and swallow the issued daily doses.

In a study conducted by Brust et al. (2010) in South Africa, the authors note that because of the increased risk in treatment failure, as a result of resistance to more than 5 MDR TB drugs, increasing the number of medications in the standardized regimen, amongst other things, could help improve treatment failure, however, the increase in the number of medications would also mean an increase in the number of tablets taken by the patients per day. This increased number of tablets will not only increase the likelihood of AEs but can certainly lead to reduced adherence.

In a meta-analysis of 19 RCT studies conducted by Nachega et al. (2014) on the pill burden and dosing frequency in Anti-Retroviral Treatment (ART), they found that pill burden was associated with lower adherence rates though the dosing frequency effect was not statistically significant. Similarly, Scott Sutton et al. (2016) also stated that a high pill burden was associated with decreased adherence to ART, supported by the findings that those who were on a single tablet (fixed dose combination) were more adherent compared to those who were on multiple tablet regimens. Though this was an ART study, these findings could be applied to the treatment of MDR TB as well, which has been reported to include up to 5 different drugs per patient. The meta-analysis also noted that adherence declined over time. The dosing frequency, however,

should not have an impact on the MDR TB treatment adherence as the treatment is taken only once per day. Another study by Scott Sutton et al (2016) reported that a high pill burden was a strong predictor of discontinuation of ART.

2.4.2. Role of HIV in MDR TB management

TB accounts for about one in four of the deaths that occur in HIV positive people. The WHO reported that the risk of developing TB in people living with HIV was 21 times higher than the risk in the rest of the world (WHO, 2017). For patients infected with MTB, HIV infection, amongst other things, was found to be a strong risk factor for the development of active TB and the composite unfavorable outcomes in MDR TB patients. It was found to be a very strong predictor for death and default but not for treatment failure (Brust et al., 2010; Reed, et al; Wells et al, 2007). Malnutrition has also been associated with HIV infection, and thus nutritional support, especially for malnourished patients with MDR TB, can improve treatment outcomes (Nair D., et al. 2017).

In a study conducted by Seung et al. (2009), in Lesotho, on the treatment outcomes of HIV positive MDR TB patients, they found that the MDR TB treatment outcomes of HIV positive patients were significantly worse compared to the HIV negative counterparts and this observation was also confirmed in a study conducted by Meressa et al (2015) in Ethiopia which noted that treatment failure or death was higher in those infected with HIV. They noted a significant mortality in the first few weeks after initiation of treatment.

Managing MDR TB and HIV co-infection is a serious challenge for clinicians, however, the development of Highly Active Antiretroviral Treatment (HAART) has significantly improved the treatment outcomes of these patients with Palacios et al. (2012) arguing that HAART confers a protective effect on mortality among patients receiving treatment for MDR TB. Early initiation of ART has been associated with reduced mortality in MDR TB patients but literature on drug interactions between MDR TB drugs and HIV drugs is not well documented yet (Meressa et al., 2015).

The development of side effects is heightened in TB patients when there is an HIV co-morbidity. HIV as a condition, for example, causes peripheral neuropathy whereas neuropathy is also a known side effect of second line TB drugs (used to treat MDR TB) and some antiretroviral drugs, e.g. Stavudine (Seung et al., 2009). In the study carried out by Brust et al., (2012) 99%

HIV co-infected patients experienced minor or mild side effects to treatment to either MDR TB treatment or HIV treatment whilst 8% of the cohort experienced serious AEs, with the most common being hearing loss and peripheral neuropathy. A study conducted by Meressa et al. (2015), also report that AEs were comparable between HIV positive and HIV negative patients, but the HIV positive individuals had a higher incidence of peripheral neuropathy.

2.4.3. Role of diabetes in MDR TB management

Several Non-communicable diseases (NCDs), such as diabetes mellitus, alcohol use disorders and smoking-related conditions, are also responsible for a significant proportion of TB cases globally (Creswell et al., 2011). In South Africa, NCDs contribute at least 33% to the burden of diseases (NDoH Strategic Plan, 2014 to 2019). NCDs put patients at increased risk of developing TB and at risk of poor treatment outcomes, however, they also present an opportunity to provide better care through increased case-detection activities, improved clinical management and better access to care for both TB and NCDs (Creswell et al, 2011).

In 2016, the WHO reported that of the 10.4 million incidence cases of TB globally, an estimated 0.8 million was attributable to diabetes (WHO, 2017). The relationship between diabetes and TB has been explored; some authors identifying diabetes as a risk factor for TB with related poor clinical outcomes in both conditions when they co-exist (Young et al, 2009). They state that there is an associated deterioration of both conditions with more severe TB symptoms and longer period of smear positivity, if these two conditions co-exists. However, in a retrospective study conducted by Singla et al. (2006) in Saudi Arabia, new cases of pulmonary TB (PTB) and diabetes comorbidity achieved higher sputum conversion rates at the end of three months treatment, compared to non-diabetic PTB patients. In contrast, a study conducted by Baghaei et al (2015) found patients with diabetes were more prone to drug resistance compared to other patients, even after adjusting for other factors.

This relationship between PTB and diabetes has been associated with an increase in drug resistant TB in diabetic patients (Bashar et al, 2001), and though a lot of studies have focused on the treatment outcomes when PTB and diabetes co-exist, only a few studies have explored the relationship between MDR TB and diabetes and the influence on MDR TB treatment outcomes. In a study conducted by Salindri et al (2016), they reported that MDR TB patients with diabetes had consistently lower rates of sputum conversion compared to MDR TB patients without

diabetes. In this study, the prevalence of MDR TB among patients with diabetes was 30.6% compared to an MDR TB prevalence of 17.7% amongst patients without diabetes. However, they reported that the risk of poor treatment outcomes was similar amongst those with and those without diabetes. This is in contrast to a study conducted by Workneh et al (2016) where they found that TB patients with diabetes were four times more likely to die compared to those without diabetes, though at baseline the two groups did not show any significant differences in clinical presentation.

2.3.4. Role of adverse events or side effects on treatment outcomes

Adverse effects can be difficult to attribute to a specific cause when a co-morbidity exists, and for MDR TB they have, at times, been the reason for changing the treatment regimen or stopping treatment temporarily or indefinitely. As stated in the SA TB Management Guidelines (2013), a patient co-infected with MDR TB and HIV poses a great challenge and requires intensive monitoring of drug interactions and additive toxicities from the treatment of both conditions, as well as treatment for alleviation and/or prevention of opportunistic infections, as the side effect profile of these medicines can sometimes overlap. Diabetes also has its own complications and the drugs used for its management also have their own side effect profile, which can overlap with the MDR TB treatment side effects/AEs.

There are several serious side effects with most MDR TB drugs, including nephrotoxicity, ototoxicity, hepatotoxicity and dysglycaemia amongst other common side effects. The management of these AEs of the treatment can have a major impact on patient adherence and completion of therapy (Meressa et al, 2015). Management of these side effects, which sometimes does not require treatment change, mean that clinicians have to prescribe adjunctive therapy to alleviate the side effects and this in turn leads to additional side effects and an increased pill burden. Brust et al. (2012), in a study of treatment outcomes of MDR TB/ HIV patients, reported an incidence of 8% of serious AEs though the majority of the patients experienced minor side effects, 38% of the cohort developed elevated thyroid stimulating hormone levels which required treatment. Thus, the presence of side effects or AEs may affect treatment adherence negatively, thus timely managements of effects and continuous clinical monitoring of patients for AEs is crucial for improved adherence (Hire et al. 2014).

CHAPTER 3: METHODS

3.1. Aim and Objectives

3.1.1. Aim

The aim of this study was to describe the clinical characteristics and treatment outcomes of MDR TB patients initiated on treatment at Nkqubela and Fort Grey Hospitals from January 2013 to June 2014.

3.1.2. Objectives

1. To describe demographic characteristics of MDR TB patients.
2. To describe clinical characteristics of MDR TB patients.
3. To describe primary treatment outcomes of MDR TB patients.
4. To determine risk factors for death, default and treatment failure among MDR TB patients.

3.2. Study design

This was a retrospective cohort study. The national electronic register for Drug Resistant (DR) TB, EDR.web, was used as a sampling frame, as it contains information of all the patients that were seen during the period under review, including their demographic and clinical information. However, for completing the data extraction sheet, the actual patient folders were used as source documents, mainly because the EDR.web database does not capture or record any information on other co-morbidities and other treatment taken, except for the HIV status of the patient.

3.4. Selection of study facility

The study facilities were chosen because they were the only two hospitals in the area that specialize in the subject of interest and they have recently been merged into one hospital in the Buffalo City Metropolitan Municipality. Both hospitals catered for both the former Transkei and former Ciskei homelands, thus the sample chosen is representative of the general population as the patients seen at the hospitals came from different backgrounds, with some coming from rural areas, others from peri-urban areas and others from urban areas. This is a real demographic representation of the Eastern Cape as a province.

3.5. Study population and sampling

The eligible study population included all MDR TB patients who were initiated on treatment at Nkqubela or Fort Grey Hospitals from January 2013 to June 2014.

An inclusive sample of all eligible patients was taken. The number of patients registered during on the EDR.web during the period under review was 928, inclusive of those with XDR TB and those that were initiated at the designated decentralized and satellite sites. The actual number of patients who met the inclusion criteria was 387, and thus the whole study population was sampled.

3.5.1. Sample selection

Inclusion criteria:

- Adults 18 years and above diagnosed with MDR TB, who were initiated on treatment at Nkqubela and Fort Grey Hospitals from January 2013 to 30 June 2014.
- Reside within the municipalities which form the drainage areas for Nkqubela and Fort Grey Hospitals.

Exclusion criteria:

- Patients who attended Nkqubela and Fort Grey Hospitals for treatment of MDR TB during the review period but were critically ill so treatment was either not initiated or continued.
- MDR TB patients who were pregnant or became pregnant during the period under review.
- Patients who died within 24 hours after MDR TB treatment initiation.

3.6. Data collection

A customized data extraction sheet was used to collect data on the patient's demographic information, clinical information and treatment outcomes (see Appendix 4).

EDR.web database was used as a preliminary source of information to populate the customized data extraction sheet. The EDR.web was used as the sampling frame as it contained the patients' personal details, when they were registered for treatment, which is also the treatment start date, their file number and also whether that particular patient was registered at Nkqubela or Fort Grey

Hospital. It was important to know beforehand where the patient was registered initially as the file numbering from both sites was the same, thus file retrieval was made easier by prior knowledge of which site the patient was registered in as the two sites were filed separately at the merged facility.

The information from the EDR.web database was then used to retrieve patient folders from archives. These folders were then used to populate the data extraction sheet, gathering information on the participants' demographic information; TB treatment history and its outcomes; HIV status and management if HIV positive; period in treatment for MDR TB (including start and end dates); laboratory tests (sputum culture and smear tests); co-morbidities; treatment details, including adjunct treatment given; treatment outcomes; and any adverse reactions/ events and their management.

The data was transcribed onto the customized data extraction sheet, as recorded on the patient's folder, without any alterations. Some variables of interest that were initially included on the data extraction sheet were not included when populating the data extraction tool either because that information was not available on the patients' folders or only a few patients had that information recorded. Some of the information not available included the average monthly income, units of alcohol consumed and the number of medication doses missed.

Data collectors, identified as five pharmacist's assistants, were used for this study. They were trained for two days on retrieving the identified patients' folders; the use of the data extraction sheet; and what information to look for on the patient folders. If clarity was required from any of the patient folders, including access to EDR.web, assistance was sought from the information officer or the Clinical Manager of the hospitals.

3.6.1. Independent variables

All the demographic characteristics (for example, age, gender, employment status, and type of residential area)

Previous TB and its outcomes

Site of current MDR TB, defined as the site where TB was located in the body.

The period in treatment

HIV status

Diabetes

Presence of other treated comorbidity besides diabetes and/ or HIV

Presence of AEs and management thereof.

Overall number of drugs taken

3.6.2. Dependent (outcome) variables

The outcome of treatment, including cure, treatment complete, treatment failure, death, default and transfer out, of MDR TB patients, with or without co-treatment for the specified comorbidities for the period under review.

3.6.2.1. Characterization of the dependent variables as per National TB Guidelines (2013)

Cure: A patient who has converted (with two consecutive negative TB cultures taken 30 days apart), and has remained TB culture negative, has completed treatment and has been consistently culture-negative for five consecutive months in the final twelve months of treatment. If one positive culture is reported during that time and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least thirty days apart. This outcome is restricted to confirmed pulmonary DR-TB patients.

Treatment completed: A patient who has completed treatment but does not meet the definition for cure due to lack of bacteriologic results (i.e. less than five cultures were performed in the final twelve months of treatment). This patient would have completed at least 18 months of treatment after culture conversion and 24 months if there was extensive lung damage at the initiation of treatment.

Death: A patient who dies from any cause while on DR-TB treatment.

Treatment default: A patient who interrupts DR-TB treatment for two or more consecutive months for any reason.

Treatment failure: A patient who has had two or more of the five consecutive cultures taken in the final twelve months and are positive, or if any one of the final three cultures are positive.

Treatment failure may be observed in patients who do not respond to treatment after 6 to 8 months of effective treatment.

Transfer Out: A patient who has been transferred to a reporting unit in another province and for whom the treatment outcome is unknown.

Cure and treatment completed were considered to be positive treatment outcomes. Death, default, treatment failure and transfer out were considered to be negative treatment outcomes. Transfer out was considered to be a negative treatment outcome as it relates to loss-to-follow-up. In this instance, once the patient was transferred out, the facility or study site did not make any follow up on the progress of the patient, thus it is unknown whether they survived, defaulted, failed or demised, hence the decision to classify as lost-to-follow up.

3.7. Data analysis

Once all the data had been collected, it was checked for completeness and then captured on an excel spreadsheet. Data cleaning was done to identify incomplete, inaccurate and irrelevant data and this data was either replaced with a logical alternative or checked against the data extraction sheet, modified or deleted. STATA version 15 (Stata Corp, College Station, TX, USA) was used for data management and statistical analysis.

Descriptive analyses were used to summarize data, measure central tendency and dispersion. Primary outcomes for the study were: cure, treatment completion, treatment failure, default and death.

Measures of association and their 95% confidence intervals were used to estimate the strength of association between the individual exposures and the outcomes in the population. Chi square tests and t-tests were used to assess whether the observed effect was statistically significant at the univariate level.

To adjust for confounding, multiple logistic regression models were used to determine significance of associations between factors associated with the individual outcomes of treatment failure, default and death whilst adjusting for confounders. Additionally, a composite outcome of poor outcomes (death, treatment failure or default versus treatment complete or cure) was also investigated for factors associated using multiple logistic regression. The independent variables investigated were chosen from those univariate associations which showed a p value ≤ 0.1 with each outcome. Intelligent manual modelling method was used to include or exclude predictors

and arrive at a final model. Significance level was set at $p=0.05$, strength of associations expressed as Odds Ratios with 95% confidence intervals.

3.7.1. Validity and Reliability

Prior to conducting the study, a pilot study was conducted, targeting 10% of the overall sample. This was used for the training of the data capturers and to identify any concerns relating to the institution's retrieval or availability rates and the completion and accuracy of the information contained in the source document. In addition to the pilot, data collectors were trained on the data collection tool and an independent person was requested to use the tool to collect the same data, in order to verify whether the data collection could be repeated using that same tool.

The data was transcribed from the patient folder onto the data extraction sheet as is, and only the investigator coded and summarised the data, with the assistance of a Biostatistician. Laboratory test results were also recorded and analysed as presented by the laboratory, where available, to ensure that conclusions made about the treatment outcomes on the patient folder corresponded with the actual laboratory results. Where no laboratory test results pages were found on the patient folder, the recorded laboratory test results on the file were considered to be accurate and were used to populate the data extraction sheet.

Sampling or selection bias was considered unlikely because the whole population meeting inclusion criteria in the specified time period was sampled. Because the sample was quite large, the likelihood of the results being due to chance was minimal. The eligibility criteria were also set clearly to avoid any confusion when sampling. The design of the study did not allow for any loss to follow up, as secondary data was used. However, those who were reported as transferred out by the facility as a final outcome, were regarded as lost to follow up as there was no further information of the disease progress or final outcome reported for such patients. Transferred out patient referred to those patients who were transferred to other sites that were not supported by Nkqubela or Fort Grey Hospitals, and these included sites within and outside the province.

Measurement or information bias was also minimised by having clear operational definitions and training the data collectors well on the use of the data extraction tool. However, the accuracy of information on the patient folder was mainly dependant on the practitioner that was attending the patient. While collecting data, the data collectors noted that there was no standard way of documenting clinical findings. Some clinicians were most likely to document the start date of

treatment, the seroconversion date and the expected date of completing treatment at every consultation, whereas others reported infrequently or did not report at all, especially the seroconversion date. This trend was also noted when reviewing the files that some information on the patient's history and clinical information was not recorded, including the treatment outcome. In such instances the researcher had to rely on information recorded on EDR.web, especially for the treatment outcomes.

In the data analysis stage, known confounders were identified and were controlled for by multivariable logistic regression analysis.

3.7.2. Generalizability

The results of this study can be generalized to the Eastern Cape population living in rural and peri-urban areas and populations similar to the population that was under study.

3.8. Ethical considerations

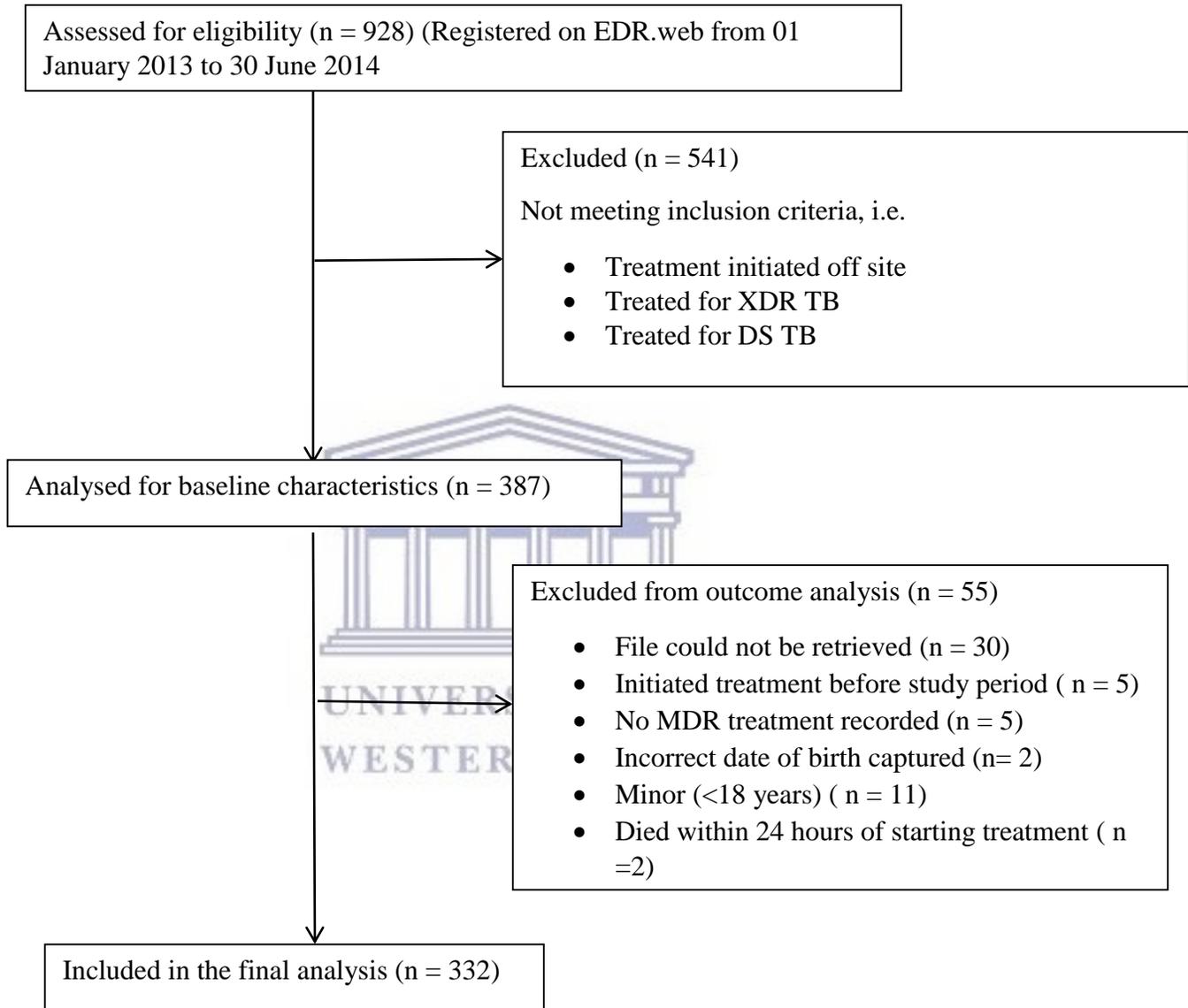
The study used secondary data which was collected for routine clinical management of the patients, thus informed consent was not required. There was no direct risk to the participants because of the study. Ethical approval to conduct the study was sought from the University of the Western Cape's (UWC's) Biomedical Research Ethics Committee (BMREC). Authorization to conduct the study in the Eastern Cape Province was obtained from the Eastern Cape Health Research Committee; and the Buffalo City Metro Health sub-district, in consultation with Nkqubela TB hospital management, granted the permission to access the facility and conduct the study there.

All patient files used were allocated a unique patient identifier to protect the identity of the patients. The standardised template with the data and patient lists from EDR.web has been kept in a safe place, under lock and key, and these will be kept there for a period of 5 years. The excel spreadsheet is password protected and only the researcher and the supervisor has access to the password.

To disseminate the results on completion of the study, a presentation of the findings will be made to the Eastern Cape Provincial Department of Health; the Buffalo City Metro Health Sub-district management; the Mdantsane Health Sub-district management and Nkqubela Hospital management.

CHAPTER 4: RESULTS

Figure 1: Flow diagram for sample inclusion



The demographic and clinical characteristics of the sample and estimates of the study population using 95% confidence intervals are presented in Table 1. The age of the sample ranged from 18 to 84 years, with the mean age of 39.4 (SD \pm 13.02). There were slightly more males, representing 57.5% (n=191), than females, who represented 42.5% (n= 141). Of the total sample analysed, 75.9% (n=252) were unemployed, 11.1% (n=37) employed and for 12.9% (n=43), their employment status was not recorded. A total of 60.2% (n=200) lived in rural areas, 35.2% (n=117) in peri-urban areas and 4.5% (n=15) in urban areas.

For the clinical characteristics reviewed, 65.1% (n=216) had previous TB, 39.5% (n=85) of those were cured, 30.2% (n=65) defaulted, 4.7% (n=10) diagnosed MDR after they were initiated on first line TB treatment, for 20.5% (n=44), first line TB treatment had failed and the results of the previous TB was reported unknown for 5.1% (n=11). In total, 259 out of 332 (78.0%) patients were diagnosed with pulmonary MDR TB whereas 18 (5.4%) had extra-pulmonary MDR TB and for 55 (16.6%) patients, their site of current TB was not recorded. Two hundred and forty five (245) (73.8%) patients were HIV positive, while 85 (25.6%) of the patients were HIV negative and there were only 2 whose HIV status was unknown (0.6%).

Diabetes was rare, with only 4.2% (n=14) of the sample recorded as diabetic, 9.9% (n=33) reported as unknown and the rest were recorded as not having diabetes. Adverse events (AEs) were reported for 40.4% (n=134), 11 (3.31%) patients with missing record of AEs, while the rest (n=187) reported no AEs (56.3%). For the last laboratory results to confirm the presence or absence of the *Mycobacterium tuberculosis*, 39.6% (n=131) presented with a negative smear and negative culture result, while some presented with either just a negative smear or a negative culture or with at least one or both of them being positive. Overall, 28.0% (n=93) of the patients were cured, 6.6% (n=22) completed treatment; 44.3% (n=147) died; 11.1% (n=37) defaulted treatment; 4.8% (n=16) failed treatment and 3.0% (n=10) were transferred out. There were also a few whose treatment outcomes were not recorded (2.1%; n= 7).

Table 1: Socio-demographic and clinical characteristics

Socio-demographic characteristics (n = 332*)	n (%; 95% CI)
Age range (years)(n)	18 - 84 (n=328)
Mean Age (years), mean, SD, 95% CI	39.4 ± 13.02, 37.88 – 40.74
Sex:	
Male	191 (57.5%; 52.11 – 62.77)
Female	141 (42.5%; 37.23 – 47.88)
Employment status:	
Employed	37 (11.1%; 8.16 – 15.03)
Unemployed	252 (76.0%; 70.98 – 80.22)
Not recorded	43 (12.9%; 9.73 – 17.03)
Type of Residence:	
Peri-urban	117 (35.2%; 30.26 – 40.56)
Rural	200 (60.2%; 54.85 – 65.39)
Urban	15 (4.5%; 2.73 – 7.38)
Clinical characteristics (n=332*)	
n (%; 95% CI)	
Previous TB:	
No	101 (30.4%; 25.69 – 35.61)
Yes	216 (65.1%; 59.75 – 70.02)
Unknown	15 (4.5%; 2.73 – 7.38)
Previous TB results (n=215):	
Cured	85 (39.5%; 33.17 – 46.27)
Defaulted	65 (30.2%; 24.42 – 36.75)
Diagnosed MDR post Rx start	10 (4.7%; 2.51 – 8.47)
Rx completed but did not seroconvert	40 (18.6%; 13.92 – 24.42)
Rx failed	4 (1.9%; 0.69 – 4.89)
Unknown	11 (5.1%; 2.84 – 9.04)
Site of current TB:	
Extra-pulmonary	18 (5.4%; 3.43 – 8.46)

Pulmonary	259 (78.0%; 73.21 – 82.16)
Unknown	55 (16.6%; 12.92 – 20.98)
Period in treatment (days), mean, SD, 95% CI	374.67 ±17.67316.7; 339.89 – 409.45
Period in Rx range (days) (n)	0 - 1492 (n=321)
HIV status:	
Negative	85 (25.6%; 21.17 – 30.60)
Positive	245 (73.8%; 68.77 – 78.27)
Unknown	2 (0.6%; 0.15 – 2.39)
Diabetic:	
Yes	14 (4.2%; 2.51 – 7.01)
No	285 (85.8%; 81.64 – 89.21)
Unknown	33 (9.9%; 7.14 – 13.67)
Recorded Adverse Events:	
Yes	134 (40.4%; 35.19 – 45.76)
None	187 (56.3%; 50.91 – 61.59)
Not Recorded	11 (3.3%; 1.84 – 5.90)
Last laboratory results:	
Culture +ve, no smear	20 (6.0%; 3.92 – 9.20)
Culture +ve, smear +ve	48 (14.5%; 11.09 – 18.74)
Culture +ve, smear -ve	15 (4.5%; 2.74 – 7.40)
Culture -ve, smear +ve	5 (1.5%; 0.63 – 3.60)
Culture -ve, smear -ve	131 (39.6%; 34.42 – 44.98)
Culture -ve, no smear	31 (9.4%; 6.65 – 13.03)
Not Recorded	39 (11.8%; 8.71 – 15.75)
Smear +ve, no culture	11 (3.3%; 1.84 – 5.92)
Smear -ve, no culture	31 (9.4%; 6.65 – 13.03)
Treatment Outcomes:	
Cured	93 (28.0%; 23.42 – 33.11)
Defaulted	37 (11.1%; 8.17 – 15.03)
Died	147 (44.3%; 39.00 – 49.69)

Not Recorded	7 (2.1%; 1.00 – 4.37)
Transferred Out	10 (3.0%; 1.62 – 5.52)
Treatment completed	22 (6.6%; 4.39 – 9.87)
Treatment failed	16 (4.8%; 2.97 – 7.74)

* except where otherwise specified

Table 2 shows further stratification of the HIV, diabetes and AE management variables. A large proportion of the HIV positive group were on ART (89%), with only 11.8% not on ART and 1.6% were not recorded whether they were on ART or not. Only 14 patients were reported to have diabetes, as shown in Table 1 above, with 14.3% (n = 2) of those presenting with Type 1, 64.3% (n = 9) presenting with Type 2 and 21.4% (n = 3) whose diabetes type was unknown. Of the 14 reported to be diabetic, only 7% (n = 1) had their HbA1c results recorded. The most common AE reported in the group was peripheral neuropathy, (10.8%, n = 36), followed by ototoxicity, 9.3% (n = 31), then hypokalaemia, 8.4% (n = 28), renal impairment, 7.5% (n = 25) and psychosis and confusion reported in 5.4% (n = 18) of the patients. In addition to the abovementioned AEs, some patients were also reported to have experienced vomiting, oral thrush, body rash, anaemia and hypothyroidism amongst others. For the management of these AEs the majority (55.2% [n=80]) of the patients continued with their treatment, while only 3.5% (n = 5) had their treatment stopped as result of AEs. The rest of the patients had their treatment changed (10.3%), treatment continued but offending drug stopped (28.3%) and only 2.8% had their treatment withheld for a while.

Table 2: HIV treatment, types of diabetes and adverse events management

Clinical characteristics	n (%)
HIV positive (n = 245)	
On HAART:	
Yes	218 (89%)
No	29 (11.8%)
Not recorded	4 (1.6%)
Diabetes (n = 14):	
Type 1	2 (14.3%)
Type 2	9 (64.3%)
Unknown	3 (21.4%)
Recorded AEs (n = 145)	
AE Management:	
Treatment changed	15 (10.3%)
Treatment continued	80 (55.2%)
Treatment continued but offending drug stopped	41 (28.3%)
Treatment withheld for that period	4 (2.8%)
Treatment stopped	5 (3.5%)

Table 3 shows the univariate associations between specific risk factors and death compared with other outcomes (default, treatment failure, treatment completed, cure and transferred out). Age, sex, employment status, type of residence, previous TB diagnosis and results, site of current TB, HIV status, diabetes and recorded AEs were analysed for their association with death. Female sex was associated with death, with 51.8% (n=73) of the females and 38.7% (n=74) of the males dying, $p=0.018$, due to MDR TB. Of the other demographic characteristics that were analysed, none were statistically significantly associated with death.

For the clinical characteristics, previous diagnosis of TB and presence of diabetes were not statistically significantly associated with death. Site of current TB was significantly associated with death, as 66.7% (n=12) of the patients who had extra-pulmonary TB died while only 39% of the pulmonary TB cases died, $p = 0.003$. A positive HIV status was also associated with death,

with 121 (49.4 %) of the HIV positive patients having died, $p = 0.006$. There was a statistically significant association between presence of AEs and death ($p=0.007$), with 53.7% ($n=72$) of those who had a recorded AE having died. Patients taking more than five non MDR drugs as well as those taking more than five drugs in total were significantly more likely to die than those taking five or less ($p=0.013$ and 0.002 respectively). However, the total number of MDR drugs was not associated with death.

Table 3: Risk factor analysis for death vs. other outcomes

Factor	Death	Other outcomes	test statistic	p-value
Age				
Age (years), mean (SD)	39.9 (37.8 - 42.1)	38.7 (36.8- 40.7)	$t=-0.815$	0.416
Sex n (%)				
Male	74 (38.7%)	117 (61.3%)	$X^2=5.58$	0.018
Female	73 (51.8%)	68 (48.2%)		
Employment status n (%)				
Employed	17 (45.9%)	20 (54.1%)	$X^2=5.38$	0.068
Not recorded	12 (27.9%)	31 (72.1%)		
Unemployed	118 (46.8%)	134 (53.2%)		
Type of residence n (%)				
Peri-urban	52 (44.4%)	65 (55.16%)	$X^2=1.64$	0.441
Rural	86 (43.0%)	114 (57.0%)		
Urban	9 (60.0%)	6 (40.0%)		
Previous TB diagnosis n (%)				
Yes	99 (45.8%)	117 (54.2%)	$X^2=1.6$	0.448

	No	40 (39.6%)	61 (60.4%)		
	Unknown	8 (53.3%)	7 (46.7%)		
Previous TB results n (%)					
	Cured	34 (40.0%)		$X^2=7.88$	0.247
	Defaulted	38 (58.5%)			
	Diagnosed MDR after Rx in.	3 (30.0%)			
	N/A	48 (41.0%)			
	Treatment completed	18 (45.0%)			
	Treatment failed	1 (25.0%)			
	Unknown	5 (45.5%)			
Site of current TB n (%)					
	Extra-pulmonary	12 (66.7%)	6 (33.3%)	$X^2=11.68$	0.003
	Pulmonary	102 (39.4)	157 (60.6%)		
	Unknown	33 (60.0%)	22 (40.0%)		
HIV status n (%)					
	Positive	121 (49.4%)	124 (50.6%)	$X^2=10.23$	0.006
	Negative	25 (29.4%)	60 (70.6%)		
	Unknown	1 (50.0%)	1 (50.0%)		
Diabetic n (%)					
	Yes	8 (57.1%)	6 (42.9%)	$X^2=3.85$	0.146
	No	120 (42.1%)	165 (57.9%)		
	Unknown	19 (57.6%)	14 (42.4%)		
Recorded AEs n (%)					

Yes	72 (53.7%)	62 (46.3%)	$X^2=10.00$	0.007
None	73 (39.0%)	114 (60.9%)		
Missing	2 (18.2%)	9 (81.8%)		
No of AEs reported n (%)				
0	78 (39.8%)	118 (60.2%)	$X^2=5.11$	0.277
1	35 (50.7%)	34 (49.3%)		
2	16 (51.6%)	15 (48.4%)		
3	11 (44.0%)	14 (56.0%)		
4	7 (63.6%)	4 (36.4%)		
No of MDR drugs n (%)				
≤ 5	105 (47.1%)	118 (52.9%)	$X^2=2.17$	0.141
>5	42 (38.5%)	67 (61.5%)		
No of non MDR drugs n (%)				
≤ 5	78 (38.8%)	123 (61.2%)	$X^2=6.18$	0.013
>5	69 (52.7%)	62 (47.3%)		
No of all drugs n (%)				
≤ 5	4 (15.4%)	22 (84.6%)	$X^2=9.54$	0.002
>5	143 (46.7%)	163 (53.3%)		

Table 4 below presents the results of univariate and multivariable logistic regression analysis of the different predictor variables on death. Only those variables that were statistically significant at the 0.1 level of significance on univariate analysis were entered in the final regression model for death. Females were 1.51 times more at risk of death due to MDR TB than males after adjusting for the other variables in the model (aOR 1.51, 95% CI 0.95-2.40), $p=0.085$. Extra-

pulmonary TB was also associated with a higher risk for death than pulmonary TB, both before and after adjusting for the confounding factors (OR: 1.344 (1.10-1.64), $p=0.003$ and aOR: 2.91 (1.03 – 8.19), $p = 0.043$). Those who were HIV positive were 1.88 times more likely to die than those who were HIV negative (OR: 2.27 (1.35 - 3.80), $p=0.002$ and aOR 1.88 (1.07 – 3.31), $p = 0.027$). Of the recorded AEs, hypokalaemia was the only one associated with death with an aOR of 2.17 (0.94 – 4.98). The patients who took more than 5 drugs in total were 3.21 times more likely to die compared to those who took 5 or less drugs, before and after adjusting for the other variables in the model (OR: 4.83 (1.62 - 14.33), $p =0.005$ and aOR 3.21 (1.02 – 10.14), $p = 0.046$).

Table 4: Logistic regression for death

Factor	Levels	Univariate analysis		Multivariable analysis	
		OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex					
	Female	1.697 (1.09 - 2.64)	0.019	1.51 (0.95 - 2.40)	0.085
Site of current TB					
	Extra-pulmonary	1.344 (1.10 - 1.64)	0.003	2.91 (1.03 - 8.19)	0.043
	Unknown			2.15 (1.16 - 4.00)	0.015
HIV status					
	Positive	2.27 (1.35 - 3.80)	0.002	1.88 (1.07 - 3.31)	0.027
	Unknown			3.57 (0.15 – 86.22)	0.433
Adverse Event					

Hypokalaemia	2.44 (1.09 - 5.46)	0.03	2.17 (0.94 – 4.98)	0.069
Number of all drugs				
>5	4.83 (1.62 – 14.33)	0.005	3.21(1.02-10.14)	0.046

When analyzing the risk factors for default, having no recorded AEs, was found to be borderline non significantly associated with default, see Table 5 below. 10 patients (2.5%) with reported AEs and 27 (14.4%) who had no reported AEs had defaulted their treatment, $p = 0.072$. The univariate results also showed that patients taking more than five drugs, including MDR TB drugs, were less likely to default treatment compared to those who took 5 or less drugs, OR 0.30 ($p = 0.01$; 95% CI 0.11 – 0.76). Taking more than 5 MDR drugs or more than 5 non MDR drugs was not statistically significantly associated with default (OR 1.00; $p = 0.96$; 95% CI 0.47 – 2.0.3; and OR 0.62; $p = 0.202$; 95% CI 0.29 – 1.29 respectively). With only one factor statistically significantly associated with default, multivariable analysis was not performed.

In that same group, when examining the outcome of treatment failure, 11 (8.2%) with recorded AEs and 5 (2.7%) with no recorded AEs had their treatment failed, $p = 0.025$, and 14 (12.8%) of those taking more than 5 MDR drugs also had their treatment failed, $p < 0.001$. Multivariable analysis, shown in Table 6, for treatment failure using blocked ears, peripheral neuropathy and dizziness (AEs) as predictors of association showed all these factors were associated with treatment failure. Blocked ears had an unadjusted OR of 14.90 (2.30 – 96.47; $p = 0.005$), whereas its adjusted OR was 9.45 (0.95-93.98; $p = 0.055$); peripheral neuropathy on the other hand had an unadjusted OR and aOR of 5.72 (1.94-16.84), $p = 0.002$ and 5.34 (1.51 – 18.92; $p = 0.009$, respectively and dizziness had an aOR of 13.05 (0.96 – 177.84, $p = 0.054$). More than 5 MDR TB drugs that a patient took was also associated with treatment failure, OR 16.28(3.63 – 73.05; $p < 0.001$) and an adjusted OR of 13.55 (2.83 – 64.86; $p = 0.001$). For the co-morbidities recorded / presented, mental health problems were associated with a higher risk of treatment failure, with an adjusted OR of 13.10 (1.10 – 155.40; $p = 0.042$). Younger age was also found to

significantly increase the risk for treatment failure after adjusting for the other factors in the model.



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Table 5: Risk factor analysis for default and treatment failure

Factor	Levels	Defaulted n (%)	p-value	Treatment failure n (%)	p-value
Age (mean difference; 95% CI)		3.36 (-1.16-7.88)	0.145	6.23 (-0.39-12.86)	0.065
Sex:					
	Male	24 (12.6%)	0.338	11 (5.8%)	0.352
	Female	13 (9.2%)		5 (3.6%)	
Employment status					
	Employed	2 (5.4%)	0.448	3 (8.1%)	0.483
	Unemployed	29 (11.5%)		12 (4.8%)	
	Not recorded	6 (13.9%)		1 (2.3%)	
Type of residence					
	Peri-urban	12 (10.3%)	0.762	5 (4.3%)	0.288
	Rural	24 (12.0%)		9 (4.5%)	
	Urban	1 (6.7%)		2 (13.3%)	
Previous TB diagnosis					
	Yes	21 (9.7%)	0.102	11 (5.1%)	0.857
	No	16 (15.8%)		4 (3.9%)	
	Unknown	0 (0.0%)		1 (6.7%)	
Previous TB results					
	Cured	8 (9.4%)	0.634	4 (4.7%)	0.466
	Defaulted	8 (12.3%)		2 (3.1%)	
	Diagnosed MDR after Rx in.	0 (0.0%)		0 (0.0%)	
	N/A	16 (13.7%)		5 (4.3%)	

Treatment completed	5 (12.5%)		3 (7.5%)	
Treatment failed	0 (0.0%)		1 (25.0%)	
Unknown	0 (0.0%)		1 (9.1%)	
Site of current TB				
Extra-pulmonary	0 (0.0%)	0.153	1 (5.6%)	0.9
Pulmonary	33 (12.7%)		13 (5.0%)	
Unknown	4 (7.3%)		2 (3.6%)	
HIV status				
Positive	27 (11.0%)	0.214	11 (4.5%)	0.9
Negative	9 (10.6%)		5 (5.9%)	
Unknown	1 (50.0%)		0	
Diabetic				
Yes	0	0.398	0	0.588
No	33 (11.6%)		15 (5.3%)	
Unknown	04 (12.1%)		1 (3.0%)	
Recorded AEs				
Yes	10 (7.5%)	0.072	11(8.2%)	0.05
None	27 (14.4%)		5 (2.7%)	
Missing	11 (10.1%)		0	
No of AEs reported n (%)				
0	27(13.8%)	0.229	6 (3.1%)	0.166
1	7 (10.1%)		4 (5.8%)	
2	0		2 (6.5%)	
3	2 (8.0%)		2 (8.0%)	
4	1 (9.1%)		2 (18.2%)	

Number of MDR drugs					
	≤ 5	25 (11.2%)	0.956	2 (0.9%)	<0.001
	> 5	12 (11.0%)		14 (12.8%)	
Number of non-MDR drugs					
	≤ 5	26 (12.9%)	0.199	12 (5.9%)	0.225
	> 5	11 (8.4%)		4 (3.1%)	
Number of all drugs					
	≤ 5	7 (26.9%)	0.008	0	
	> 5	30 (9.8%)		16 (5.2%)	0.232

Table 6: Logistic regression for treatment failure

Factor	Levels	Univariate analysis		Multivariable analysis	
		OR (95% CI)	p-value	aOR (95% CI)	p-value
Age (years)		0.96 (0.92 - 1.00)	0.065	0.95 (0.90 - 1.00)	0.040
Number of MDR drugs	> 5	2.03 (1.49 - 2.76)	< 0.001	13.55 (2.83 - 64.86)	0.001
Co-morbidities:					
	Epilepsy	4.87 (0.96 - 24.70)	0.056		
	MHCU	11.14 (1.88 - 66.04)	0.008	13.10 (1.10 - 155.40)	0.042
Adverse Event					

Blocked ears (tinnitus)	14.90 (2.30 - 96.47)	0.005	9.45 (0.95 – 93.98)	0.055
PN	5.72 (1.94 - 16.84)	0.002	5.34 (1.51- 18.92)	0.009
Dizziness	6.96 (0.68 – 70.90)	0.102	13.05 (0.96 – 177.84)	0.054

A further composite outcome was defined as either positive or negative outcome. Positive outcomes including those patients who were cured or completed treatment. Negative outcomes included all the other outcomes. Univariate analysis for sex, HIV status, AEs (nausea, renal impairment, hypokalaemia and hypothyroidism), number of all drugs taken, number of MDR TB drugs taken and number of non-MDR TB drugs was done, see Table 7 below. However, only HIV status, nausea, renal impairment, hypothyroidism and number of all drugs taken were included in the final model. Those who were HIV positive were 2.02 times more likely to have negative outcomes compared to those who were HIV negative, after adjusting for the other variables in the model, aOR 2.02 (1.18 -3.47; p = 0.010) (OR: 2.15 (1.30-3.57; p=0.003). Taking more than 5 drugs in total was not statistically significantly associated with poor outcomes, adjusted OR of 1.94 (0.81 – 4.61; p = 0.136). Nausea and hypothyroidism were inversely associated with poor outcomes, with those patients having these AEs being less likely to experience poor outcomes OR: 0.10 (0.01-0.88; p=0.038) and OR: 0.20 (0.04-1.07; p=0.06), respectively. After adjusting for confounders, aOR: 0.06 (0.01-0.59; p=0.016) and aOR: 0.16 (0.03-0.87; p=0.033), respectively. However, having renal impairment was a risk for developing poor outcomes, both before and after adjusting for confounders, OR: 2.97 (0.99-8.88; p=0.051) and an aOR: 3.65 (1.02-13.11; p=0.047).

Table 7: Logistic regression for negative outcomes vs. positive outcomes

Factor	levels	Univariate analysis		Multivariable analysis	
		OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex:					
	Female	1.54 (0.97-2.46)	0.068		
HIV status:					
	Positive	2.15 (1.30-3.57)	0.003	2.02 (1.18-3.47)	0.010
Adverse Event					
	Nausea	0.10 (0.01-0.88)	0.038	0.06 (0.01-0.59)	0.016
	Renal Impairment	2.97 (0.99-8.88)	0.051	3.65 (1.02-13.11)	0.047
	Hypokalaemia	3.45 (1.17-10.20)	0.025		
	Hypothyroidism	0.20 (0.04-1.07)	0.06	0.16 (0.03-0.87)	0.033
Number MDR TB drugs taken	>5	1.26 (0.77-2.05)	0.357		
Number of non MDR TB drugs taken	>5	1.43 (0.90 - 2.30)	0.133		
Number of all drugs taken	>5	2.37 (1.06 - 5.30)	0.036	1.94 (0.81 – 4.61)	0.136

CHAPTER 5: DISCUSSION

5.1. Introduction

This section discusses the major findings of this study in the light of relevant literature. The section commences with discussing socio-demographic characteristics, to give an insight into who these patients were and how they lived. It is followed by a discussion of the treatment outcomes and, what they mean in relation to the “End TB Strategy”. The section will then conclude with the discussion about the clinical characteristics associated with MDR TB, divided into sub-headings, focusing mainly on those factors that were statistically significantly associated with the individual outcomes of interest, or were just factors of interest.

5.2. Socio-demographic characteristics

The results obtained from this study show that the patients seen at the two hospitals during the period under review had a mean age of 39 years, reflecting an age group that is most vulnerable to contracting MDR TB. Similar studies by Schnippel et al. (2015) and Cox et al. (2015) undertaken in South Africa, have also shown mean ages of 35 years and 30 years respectively, to be vulnerable to contracting MDR TB.

The majority of the patients in this study, 75.9%, were unemployed, a finding which is in agreement with the statement that TB is a disease of the poor (Dong et al., 2007). In fact, Dong et al. (2007), have previously reported that poverty “fuels desperate behaviour, including intentional non-adherence to ART and TB treatment and voluntary sacrifice of health in order to retain social grants”. In this study, approximately 30% of the participants were reported to have defaulted previous TB treatment. Statistics SA (2017) reported that poverty affected mostly people from the rural areas, such as the Eastern Cape and Limpopo and those with little or no education. The socio-demographic factors stated above are discussed in this chapter in relation to MDR TB and this gives a better understanding of the relationship between TB and these factors.

The unemployment rate of 75.9% in this study is very high, and contrasts with what Kendall et al., (2013) reported when they conducted a similar study in the rural Western Cape in which only 36% of their study population was unemployed. Whilst it might appear that 36% of unemployment is lower in the Western Cape is lower than the 76% in the Eastern Cape, this prevalence is still higher than the national unemployment rate of 27.7%, as reported by Statistics

SA (2017). Moreover, both these prevalences are higher than those reported in Stats SA (2017) suggesting overall unemployment rates in the Eastern and Western Cape provinces to be 35.5% and 21.9%, respectively (StatsSA, 2017).

Though this study found no association between employment and death due to MDR TB. The high unemployment rate reported in this study population highlights the need to consider social determinants of health when addressing MDR TB, a communicable disease. Addressing these social determinants is one of the nine important priorities for the NDP 2030 vision. As such, doing this would take us a step further not only in reducing TB infections but also reducing the prevalence of other communicable diseases to promote health of the general South African population (Boutayeb 2006).

Current programmes to reduce the spread of TB should not only focus on peri-urban areas and/or informal settlements but should include the rural areas as well and an emphasis on addressing social determinants of health, as alluded to above. Understandably, people migrate from rural areas to urban and peri-urban areas, however, once these migrants have fallen sick in their places of work, they usually return home to be cared for by their relatives, who might, be illiterate (Clark et al., 2007). Although literacy did not form part of the initial research question, it appears to play an important role in the spread of TB and the relationship between literacy and TB was noted in Yemen where the authors found that lower levels of literacy were related to diagnostic delay of TB (Date & Okita, 2005).

The characteristics of these two countries are rather different, however, a meta-analysis of gender-related differences in barriers and delays that limit access to TB diagnostic and treatment services by Krishnan et al (2014) also noted that lower health literacy levels were correlated with greater fear of TB. Marimwe & Dowse (2017), in a study on health literacy from a small Eastern Cape Town, also reported that a third of the study participants reported always requiring help when reading general health information. Though literacy was not the sole determinant of health literacy especially in low education population (Marimwe & Dowse, 2017), Statistics SA (2017) reported that South Africa had a 14.6% functional illiteracy and that at least 5.9% of persons 20 years and older in the Eastern Cape had no schooling at all in the year 2016. This could then mean that caregivers may not fully understand how the disease presents itself and its implications in one's health. This point is confirmed by Maharaj et al (2016) who found that 26.6% of the

respondents in their study believed that MDR TB was caused or spread by witchcraft and that it was a punishment from God. Respondents from Cramm et al. (2010) believed that TB was an African disease that led to HIV. In the study by Maharaj et al (2016), some respondents believed that MDR TB could be transmitted through sexual intercourse, kissing or touching, and although the majority knew that treatment would take up to 24 months, some believed that it would take just 6 months to complete treatment. Some respondents also mentioned that if they felt better or worse, they would stop taking treatment (Maharaj et al., 2016; Cramm et al., 2010).

The high default rate (11.1%) reported in this study, although not explored further, could have been influenced by the views expressed in the studies mentioned above. Literacy was, however, not measured in this study because this was a record review and this information was not available in the patient files as it does not constitute routine information required for registration. However, the socio-demographics of the study population tend to point towards low levels of literacy (poverty, unemployment, etc.) therefore further primary epidemiological studies of the socio-economic determinants of poor outcomes in MDR TB using patient interviews are warranted in this population.

The views expressed in the studies mentioned above are relatively disturbing but may provide some insights into why the disease is spreading in the manner that it is and that may also elucidate why some patients would, after discharge from the hospital, rather default treatment, to return later with a more complex disease, with some patients dying at home. The abovementioned studies have also touched on the subject of discrimination and fear of stigma. All the aforementioned factors, including stigma should be the main focal areas when educating patients, caregivers and the community about TB, MDR TB and its complications.

Of concern was the fact that women, perceived to be primary caregivers, were 1.52 times more likely to die from MDR TB compared to men. These results are in contrast with other studies that reported women to be more vigilant about their health status and more likely to adhere to treatment compared to men (Jain et al. 2014). However, they were similar to the results of Franke et al. (2008) that suggest women to be more likely to die at a higher rate than men possibly because women are usually poorer and most disadvantaged in the households.

5.3. Clinical Characteristics and Treatment Outcomes

The cure rate and the proportion of patients that completed treatment in this study was quite low. Though this study was conducted only amongst patients who were admitted at the hospitals. This could be a small fraction of the patients that were seen for MDR TB during that treatment period. However, these findings reflect a failing TB management programme in the Eastern Cape province and an increasing XDR TB caseload, which is more expensive and more difficult condition to treat than MDR TB (Jacobson et al. 2010). The cure rate of 28% reported in this study is lower than the prevalence of 41% and 51% reported in studies conducted in KwaZulu-Natal by Brust et al (2010) and in Khayelitsha by Cox et al (2015), respectively.

While the cure rate obtained in this study is similar to 29.8% obtained in a study of HIV co-infected MDR TB patients conducted by Umanah et al (2015) at Sizwe Tropical Disease Hospital in Johannesburg, it is lower than the 39.4% cure rate (though confounded by presence of XDR TB (9.8% of population)) reported by Schnippel et al (2015) in a study on predictors of mortality and treatment success during treatment for rifampicin-resistant tuberculosis within the South African National TB Programme. Similarly to the study by Umanah et al (2015), 73.8% of patients in this study were HIV positive. The treatment success rate in this study is also far lower than the target set in the SA NDoH national strategic plan, which has a set target of over 65% MDR treatment success rate by 2018/2019, and this value also remains lower than the 42% baseline the department had for the year 2013/2014, which was the year under review (SADoH, 2014).

The low cure rate observed in this study could have been due to a number of factors, including the clinical condition in which the patient presented with at initial diagnosis, which led hospital admission, but such an investigation was beyond the scope of this paper, thus further research is needed in order to ascertain whether a relationship exists. Though not assessed in this study, Elliot et al. (2014) reported that the weight of the patient at MDR TB diagnosis and adherence to oral MDR TB medication were associated with unfavorable treatment outcomes but a positive smear result at diagnosis (one of the reasons for admission during treatment) and HIV positive status of the patient were not associated with unfavorable outcomes.

Only 6.6% of the patients were reported to have completed treatment during the period under review. This result however, is higher than the 3% of patients reported to have completed

treatment in the KZN by Brust et al (2010). However, the cure rate in the Brust et al (2010) study was reported higher. The results reported in this study and the study mentioned above, however, differ quite significantly from the 16.5% treatment completion reported by Umanah et al (2015) on predictors of cure among HIV co-infected MDR TB patients at a hospital in Johannesburg, South Africa, noting that the population in this study was mainly from the rural areas and they had been admitted at the Nkqubela Hospital for initiation on MDR TB treatment but presenting with different clinical pictures.

Cure and treatment completed were regarded as positive outcomes and this was approximately 35%, a low proportion compared to a study conducted by Kurbatova et al (2012) where the percentage of patients who had positive treatment outcomes for MDR TB treatment was 65%, a result similar to the pooled result of 64% reported in a meta-analysis by Orenstein, et al (2009), with both studies presenting a different socio-demographic profile, compared to this study.

The negative treatment outcomes accounted for 65.1% of the final outcomes, with death accounting for 44.3%, default accounting for 11.1%, treatment failed accounting for 4.8% and transfer out accounting for 3%. This again is in contrast to the findings made by Cox et al (2015) where the authors reported that death, default and treatment failure accounted for 14%, 32% and 3%, respectively and Schnippel et al (2015) reporting death, loss to follow up and treatment failure at 27.8%, 23.7% and 9.3%, respectively, in their respective populations. The differences in the results obtained in the abovementioned studies and this study could be due to the fact that both Cox et al (2015) and Schnippel et al (2015) included all patients registered on the database, irrespective of site of initiation, whereas this study focused only on patients that were initiated at the site under review.

The high percentage of subjects who had died in this study is of concern as it directly impacts on South Africa's realization of the 90/90/90 vision and the percentage is once more much higher than that reported in the Sizwe Tropical Disease Hospital study and the KZN MDR study, which both reported a death rate of 22.7% and 18%, respectively (Umanah et al., 2015 & Brust et al., 2010). What is not clear from the study is what the baseline clinical condition was at first presentation and what were the reasons for admission if not all cases necessitated admission, and answers to these questions could better explain the reason for the results obtained.

5.3.1. HIV, Diabetes and Adverse events management

In an attempt to understand the clinical characteristics that the patients presented at baseline, the effect of HIV, diabetes and AEs, amongst other things, on treatment outcomes was explored in this study.

5.3.1.1. HIV

The SA National TB Guidelines (2013) stipulates that all co-infected MDR/XDR-TB/HIV patients qualify to receive antiretroviral therapy (ART) regardless of their CD4 count. The presence of HIV increased the risk of death by 2.27 fold compared to those patients who were HIV negative. In this study, 73.8% of the population was HIV positive, with 89% of that HIV positive population on ART, a percentage that is not surprising considering the gains that South Africa has enjoyed since the scale up of HIV diagnosis and treatment. As a result of the scale up, the country reported a four-fold increase in the number of people receiving ART in the year 2009 and 2012 and the baseline TB/HIV co-infected client initiated on ART rate was 54% in 2014, an amount lower than that reported in this study (SA NDoH Strategic Plan, 2014). The 73.8% HIV positive population observed in this study is similar to a population observed by Loveday et al (2015); Cox et al (2015) and Schnippel et al. (2015) reported that HIV co-infected patients not on ART were two times more likely to die compared to those who were on ART.

It is important to note that the period under study was before the current “test and treat” approach that the country has adopted, and thus it is expected that with this new approach the percentage of HIV positive patients who would be on ART today would be higher than this and thus an increased chance of survival, as seen in the study by Umanah et al (2015), where males who were initiated on ART prior to initiating MDR TB treatment were likely to be cured. However, disparities due to sex will have to be taken into consideration when a decision is to be made as the same study found that females were more likely to be cured if ART is initiated post MDR TB treatment initiation.

5.3.1.2. Diabetes

The presence of diabetes was modest in this study, with only 4.2% of the subjects reported as having diabetes, and this is similar to the 4% reported by Kendall et al (2013) in a retrospective cohort study conducted in the Western Cape and 5% reported by Rheeder et al (2017) in a study

about NCD outcomes of PHC screening in 2 rural subdistricts of the Eastern Cape. This estimate also compares fairly to the 4.5% type 2 diabetes prevalence in SA reported by IDF (2009). This finding is quite unexpected considering that Type 2 Diabetes is a disease of lifestyle, with recent studies also implicating communicable disease like HIV in the escalating increase in NCDs, including diabetes (Todowede & Sartorius, 2017). In 2011 Levitt et al. reported that about 13 million South Africans were physically inactive or insufficiently active, with 9.1 million overweight or obese. At the time of the study, adolescents were already presenting with NCD risk profile. A study conducted in the Nkonkobe Municipality of the Eastern Cape found that the combined prevalence of obesity and overweight was as high as 57% in that rural region, a region that also refers patients to Nkqubela hospital for MDR TB management. This rise in obesity is associated with an increased risk of NCDs (Otang-Mbeng et al, 2017). The low proportion of diabetes reported in this study could be due the age of the study population, as the mean age was reported to be 39 years (95% CI 37.88 - 40.74 years). Type 2 diabetes, reported to be more prevalent (64.3% of the diabetics) in this study, has been associated with older age, amongst other risk factors (WHO, 2016).

Further exploration of co-existence of diabetes with MDR TB is needed, as shown in a study done in Mexico for evaluating the effect of Type 2 Diabetes on TB drug resistance. In this study, the authors note that diabetic patients were more likely to present with MDR TB, have treatment failure and were at risk of relapse (Perez-Navarro et al, 2017). Though the population is different to the population used in this study, with the diabetic patients reported to be at least 10 years (49.7+-11.4) older than the non-diabetic patients (38.6+-17.4), further exploration could prove beneficial for better management and screening of both conditions even here in South Africa.

5.3.1.3. Adverse events

For recorded AEs, 43.7% of the population reported to have experienced one or more AEs to the treatment. Only 3.5% of those who experienced AEs necessitated the treatment to be stopped, while 55.2% continued their treatment. Of patients who were reported to have had AEs, 53.7% died, with hypokalaemia associated with 2.32 times the risk of death compared to other AEs, when controlling for confounders. However, only 7.5% and 8.2% with reported AEs defaulted and failed treatment, respectively, thus indicating that the presence of AEs was marginally associated with default or treatment failure. Of the AEs reported in relation to treatment failure,

blocked ears, dizziness and peripheral neuropathy presented with the highest odds of treatment failure compared to other AEs.

Brust et al. (2012) in a study on integrated, home-based treatment for MDR TB and HIV in rural South Africa, reported an incidence of 8% of serious AEs though the majority of the patients experienced minor AEs, 38% of the cohort developed elevated thyroid stimulating hormone levels which required treatment. Ototoxicity and peripheral neuropathy have been reported in other studies to be the reasons for stopping, reducing frequency or changing treatment in MDR TB patients (Bhardwaj et al. 2015; Wu et al. 2016; Nathanson et al. 2004). Similarly, ototoxicity and peripheral neuropathy were reported to be amongst the most common AEs reported in this study. In a study conducted by Deshmuck et al. (2015) to explore the reasons for loss to follow up in MDR TB treatment in India, some respondents reported AEs as an important barrier for treatment adherence and were an important reason to discontinue treatment. Thus, the presence of side effects or AEs may affect treatment adherence negatively, thus timely managements of effects and continuous clinical monitoring of patients for AEs is crucial for improved adherence.

5.3.1.4. Number of drugs

In this study, the number of drugs the patient takes was associated with death and treatment failure. It was found that patients taking more than five drugs in total, including MDR TB and non MDR TB drugs were more likely to die compared to those who took five or less total drugs. For treatment failure, those taking more than five MDR TB drugs were reported to be more likely to fail treatment than those taking five or less MDR TB drugs. The issue of pill burden in MDR TB has not been greatly explored, however, in a study conducted by Chakaya et al (2008), pill burden, amongst other things, was identified as one of the challenges to HIV/TB care. On the other hand, in a study on polypharmacy and medication adherence in patients with type 2 diabetes, the authors found the total number of medicines prescribed was not directly correlated with medication adherence but rather adherence was lower for medicines not felt to be improving current or future health in that sample (Grant et al., 2003).

In a study by Nachege et al (2014) the authors reported that a higher pill burden was associated with reduced adherence to treatment, which has been identified as critical factor in MDR TB management (Nathanson et al., 2004; SA National TB Guidelines, 2013). In a study conducted by Brust et al. (2010) in South Africa, the authors also noted that because of the increased risk in

treatment failure, as a result of resistance to more than five MDR TB drugs, increasing the number of medications in the standardized regimen, amongst other things, could help improve treatment failure. However, as observed in this study, an increase in the number of drugs is not only associated with treatment failure but also with death.

5.3.1.5 Previous TB diagnosis

A large proportion (65.1 %) of the patients in this study were reported to have had TB previously and 20.4% of those had failed first line treatment, hence the MDR TB diagnosis. This is slightly higher than the percentage of patients with previous TB reported in a study conducted in KZN by Maharaj et al (2016) but lower than that reported by Schnippel et al (2015) in the study on the South African National TB programme. These findings point to the need to strengthen the management of drug susceptible TB and also increase case detection and follow up of TB contacts once a patient presents at the facility with TB or symptoms thereof. Although a previous TB diagnosis was not associated with death, default or treatment failure in this study. The need to treat TB correctly cannot be emphasized enough, as getting it right the first time would ensure that the incidence of MDR TB infection is greatly reduced.

5.4. Limitations of the study

The accuracy of the data could not be confirmed as the study was using secondary data. Additionally the possibility of misclassification and measurement bias was greater because the data was not specifically collected for the purposes of this study but rather for routine management of the patients. Also, any missing data might have impacted the ability of the researcher to detect associations between outcomes and certain variables.

Upon discharge from the hospital, on completion of the intensive phase, patients might have developed other comorbidities and sought treatment in other facilities close to their residential area, and this might not have been reported to the MDR TB site, and this would also affect the treatment outcomes. Thus the findings of this study can only be generalised to the intensive phase of treatment.

There were only a few patients with recorded CD4 count or viral load percentages during treatment, which then limited the understanding of whether initiation or treatment of MDR TB

had any significant effect on the CD4 count, as a low CD4 count was considered as a predictor of poor treatment outcomes in MDR TB patients (Umanah et al., 2015).

Because of the retrospective nature of the study, one cannot ascertain what occurred first, the outcomes or the exposure, for example, the number of all drugs taken or the treatment failure. This phenomenon of reverse causality limits the interpretation of risk factors for outcomes in such a study design.



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CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The findings from this study demonstrate a struggling TB control programme in the Eastern Cape Province. The treatment success rate and cure rate reported in this study are much lower than reported in other studies conducted in similar settings around South Africa and the death rate is also much higher compared to other parts of the country. These findings could be due to a number of factors, considering that the patients included in the study were initially admitted at the hospital for initiation of treatment, with differing clinical presentations. Further exploration of this was, however, beyond the scope of this paper but could be considered for future research.

A large proportion of patients in this study were unemployed and lived in rural areas, thus highlighting the role played by these social determinants on the MDR TB treatment outcomes.

Though diabetes was rare in this sample, the literature clearly highlights the relationship between these two conditions and thus, further research is required in this setting to explore this further.

This study also reported a high percentage of patients who were previously treated for TB and although this was not significantly associated with the negative treatment outcomes. These findings point to the need to strengthen the management of drug susceptible TB and also increase case detection and follow up of TB contacts once a patient presents at the facility with TB or symptoms thereof.

The risk factors for death identified in this study included the site of current TB, a positive HIV status, the presence of AEs, taking more than five drugs and the female gender. Further research is warranted to explore these factors further.

Recommendations

There needs to be an increase case detection activities of patients with both drug susceptible TB and MDR TB and efforts should be made to ensure that TB contacts in households are identified, screened and initiated on treatment timeously. A large proportion of patients included in the study had previous TB and quite a significant number defaulted treatment, thus, retention in care should be greatly emphasised for those on treatment and more efforts should be made by healthcare workers to trace those who have been diagnosed and initiated on treatment, especially after discharge from the hospital.

Although no statistically significant relationship was noted between diabetes and MDR TB in the study, further research and monitoring is required when the two conditions co-exist in a patient. The up scaling of diabetes and other NCD management, allowing for inclusion of management in treatment indicators or reports, e.g. reporting on the number of known diabetic patients who have had their HbA1c bloods taken in the last six months, is needed, because though diabetes was rare in this study, only one patient had their HbA1c results reported.

The presence of AEs should be monitored closely and continuously and once identified, should be managed accordingly and the patient reassured. Development of shorter regimens is currently underway, however, a regimen requiring less tablets to be taken is also required. The reduced pill burden could prove quite beneficial for these patients, as it has been noted in ART patients taking a single dose regimen.

There needs to be regular viral load and CD4 counts analysis conducted for patients on ART in order to detect those whose ART regimen is currently failing, as this will have a negative impact on the treatment outcomes and the realization of the 90-90-90 goal.

Future research

Studies could explore:

Follow up patients from MDR TB treatment site at their own clinic setting to completion of treatment. These patients can be followed up from discharge to treatment end date reviewing treatment for TB and other co-morbidities that were pre-identified or that were identified after discharge from the specialised hospital.

Challenges and successes in the use of decentralized and satellite sites for DR TB.

Impact of specific drug resistance pattern to the treatment outcomes observed in this study, e.g., treatment with moxifloxacin.

Diabetes impact on culture conversion and final outcome in MDR TB patients.



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APPENDICES

Appendix 1: Ethics approval from UWC's Ethics Committee



OFFICE OF THE DIRECTOR: RESEARCH RESEARCH AND INNOVATION DIVISION

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South Africa
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www.uwc.ac.za

19 January 2017

Ms O Jikijela
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM/17/1/30

Project Title: Clinical characteristics and treatment outcomes of Multi-drug Resistant Tuberculosis patients attending a hospital in Buffalo City Metropolitan Municipality, Eastern Cape.

Approval Period: 15 December 2016 – 15 December 2017

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval. Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

A handwritten signature in black ink that reads 'Josias'.

*Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape*

PROVISIONAL REC NUMBER -130416-050

Appendix 2: Approval to conduct study from Eastern Cape Department of Health



Eastern Cape Department of Health

Enquiries: Madoda Xokwe Tel No: 040 608 0856

Date: 27 February 2017 Fax No: 043 642 1409 e-mail address: madoda.xokwe@ehealth.gov.za

Dear Ms. O. Jikijela

Re: Clinical characteristics and treatment outcomes of Multi-Drug Resistant Tuberculosis patients attending a hospital in Buffalo City Metropolitan Municipality, Eastern Cape (EC_2017RP8_697)

The Department of Health would like to inform you that your application for conducting a research on the abovementioned topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.
2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.
3. The Department of Health expects you to provide a progress on your study every 3 months (from date you received this letter) in writing.
4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Epidemiological Research & Surveillance Management. You may be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.



SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE



UNIVERSITY *of the*
WESTERN CAPE

Appendix 3: Permission to conduct research by Buffalo City Metro Health subdistrict



Province of the
EASTERN CAPE
HEALTH

BUFFALO CITY METRO HEALTH DISTRICT

OFFICE OF THE DISTRICT MANAGER

18 Sheffield Road • Westbank • East London • 5200, Eastern Cape
Private Bag X 9015 • Main Post Office, East London • 5200 • Eastern Cape
Tel.: +27 (0)43 708 1797 • Fax: +27 (0)43 708 1836/ 086 245 5023 • Website: www.ecdoh.gov.za
Enquiries: Ms Z Mntuyedwa

INTERNAL MEMORANDUM

To:	CEO: Nkqubela TB Hospital
From:	District Manager
Subject:	Permission to conduct Research Study: Ms Olwethu Jikijela
Date:	4 April 2017

Purpose

The purpose of this memorandum is to inform relevant Buffalo City Health District staff and patients of permission granted on research study to be conducted by Ms Olwethu Jikijela.

Background and Exposition of Facts

Olwethu Jikijela is doing her Masters in Public Health with the University of Western Cape. The title of the research study is **Clinical Characteristics and Treatment Outcomes of Multi-Drug Resistant Tuberculosis Patients attending Nkqubela Hospital.**

Olwethu Jikijela has requested for permission to do research in Buffalo City Metro Health District in the following facility: Nkqubela TB Hospital in Mdantsane and has submitted all the required documents for a research study in the Eastern Cape Department of Health facilities and as such permission has been granted to her by the Research unit to conduct the study in terms of her research protocol and methodology.

United in achieving quality health care for all

Fraud prevention line: 0800 701 701
24 hour Call Centre: 0800 032 364
Website: www.ecdoh.gov.za



Appendix 4: Data extraction tool

A. DEMOGRAPHIC INFORMATION

1. Hospital folder number: _____

2. Age (Date of birth): Date Month Year

3. Sex:

3.1. Male

3.2. Female

4. Employment status:

4.1. Employed

4.2. Unemployed

4.3. Not recorded

5. Average monthly income: _____

6. No of documented alcohol glasses taken per day: _____

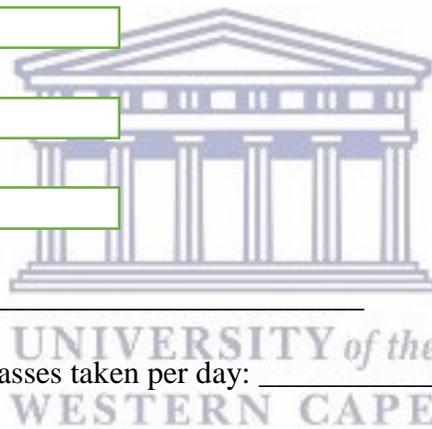
7. Place of residence: _____

8. Type:

8.1. Urban

8.2. Rural

9. Referring site: _____



B. CLINICAL INFORMATION

10. Previous TB diagnosis:

10.1. Yes

10.2. No

10.3. Unknown

11. If yes, treatment completed:

11.1. Yes

11.2. No

11.3. Unknown

12. Results of previous treatment:

12.1. Cured

12.2. Treatment completed but failed to seroconvert

12.3. Defaulted

12.4. Lost to follow up

12.5. Unknown

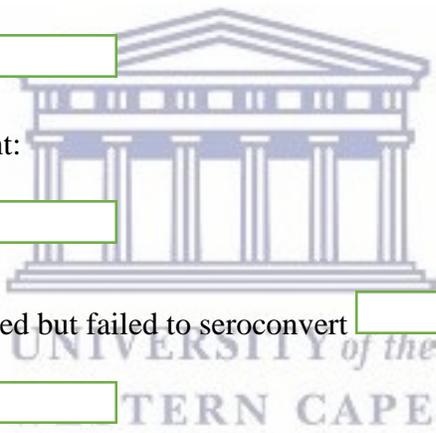
13. If no previous TB diagnosis, is it a TB contact?

13.1. Yes

13.2. No

14. Site of previous TB:

14.1. Pulmonary



14.2. Extra-pulmonary

14.3. Unknown

15. Site of current TB:

15.1. Pulmonary

15.2. Extra-pulmonary

15.3. Unknown

16. Current treatment for MDR TB: _____

17. Period in treatment for MDR TB:

17.1. Date started

17.2. Date seroconverted

17.3. Date ended



18. HIV status:

18.1. Positive

18.2. Negative

18.3. Unknown

19. If HIV positive:

19.1. CD4 count at initiation of MDR TB treatment: _____

19.2. Last CD4 count recorded while on MDR TB treatment: _____

20. On HAART:

20.1. Yes

20.2. No

20.3. Unknown

21. Date of initiation of HAART, if known: _____

22. Regimen: _____

23. Diabetic:

23.1. Yes

23.2. No

23.3. Unknown

24. If yes above, specify type: _____

25. HbA1c results done in the past year: _____

26. Other co-morbidities recorded: _____



27. Current treatment for Diabetes: _____

28. Other treatment taken: _____

29. Recorded adverse events: _____

30. Recorded management of the adverse events:

30.1. Treatment changed

30.2. Treatment withheld for that period

30.3. Treatment stopped

30.4. Treatment continued

31. Last 2 laboratory results done/received:

32. No. of doses missed, as recorded on the DOTs card, if available:

C. TREATMENT OUTCOMES

33. Recorded treatment outcomes:

33.1. Cured

33.2. Treatment completed

33.3. Treatment failed

33.4. Defaulted

33.5. Died

33.6. Transferred out

