Outpatient treatment of Drug-resistant Tuberculosis in a Hyperendemic Setting

by

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Declaration

I, Dr Jashen Pillay, Student no. 208501921 (candidate), Dr Strinivasen Gounden (Supervisor), Dhiren Sadhabiriss (Co-Supervisor) and Professor Nombulelo Magula (Co-Supervisor) declare that:

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Abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Anti-retroviral therapy
ATT	Anti-tuberculosis treatment
AUC	Area under the curve
BREC	Biomedical Research Ethics Committee
BDQ	Bedaquiline
CFZ	Clofazimine
DST	Drug-susceptibility testing
EMB	Ethambutol
EPTB	Extra-pulmonary tuberculosis
GIT	Gastrointestinal Tract
GXP	GeneXpert
HIV	Human Immunodeficiency Virus
INH	Isoniazid
KZN	KwaZulu-Natal
LAM	Lipoarabinomannan; Latin American Mediterranean
LFX	Levofloxacin
LZD	Linezolid
MDR-TB	Multidrug drug-resistant tuberculosis
MDR/RR-TB	Multidrug-resistant/Rifampicin-resistant tuberculosis
MFX	Moxifloxacin
MTB	Mycobacterium tuberculosis
NIH	National Institute of Health
PAS	p-aminosalicylic acid
RIF	Rifampicin
SPSS	Statistical Package for the Social Sciences
STREAM	Standardisation of treatment for Multidrug-resistant tuberculosis
T	Terizidone
TB	Tuberculosis
UKZN	University of KwaZulu-Natal
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

Abstract

Background: *The existence of multidrug-resistant tuberculosis (MDR-TB) represents a failure of effective infection control. There are over half a million new cases diagnosed annually with treatment success rates of only 57% reported in 2019. These numbers are highest in hyperendemic regions of the world, including South Africa, which has a high burden of tuberculosis and HIV co-infection. Treatment of MDR-TB is challenging and is usually managed at specialised centres. There is currently a transition into the decentralised treatment of MDR-TB for outpatients. Describing the features of DR-TB may influence improved treatment strategies for the future.*

Objectives: *To determine the prevalence of DR-TB at a single, central outpatient site in a hyperendemic area of South Africa, and to evaluate known risk factors and their relationship with outcomes, including time between diagnosis and treatment initiation.*

Methods: *A retrospective chart review of all new cases of DR-TB referred to a central hospital in Durban for outpatient care for the period 01/01/2017 to 31/03/2017 was conducted. Data included demographics, co-morbidities, time-to-treatment, treatment adverse effects and outcomes and were collected and collated from physical charts and the computerised registry. The data was then analysed using SPSS software.*

Results: *The period prevalence of MDR-TB at the site was 44 cases/100 000 population. Of these cases, one hundred and eleven new cases of DR-TB were included in the analysis which comprised 57 (51.35%) males. Most patients were of African ethnicity (n = 107, 96.4%). Thirty-one (27.9%) patients did not have HIV co-infection. More than one-half of patients (n = 56, 51.5%) had a history of TB and was significantly higher in males than in females (n = 34, 59.6%) and n = 22, 40.7%) respectively; p= 0.020). Five (4.5%) patients had co-morbidities of hypertension, diabetes mellitus, or renal impairment. Most patients (n = 98, 88.3%) were treated within three months of diagnosis. The mean time-to-treatment was significantly longer in patients with extrapulmonary DR-TB (150.14 (±175.90) days compared to 53.21 (±66.01) days; p-value=0.002). Significantly more patients were treated within 6 weeks if they had a positive GeneXpert test (n = 35, 89.7% compared to n = 11, 17.5%, p=0.013). Fifty-one different treatment regimens were used, and 139 side-effects were reported, the most common being ototoxicity, hypothyroidism and peripheral neuropathy. Eighty-two (73.87%) patients completed follow-up until cure.*

Conclusion: *The high burden of TB and HIV co-infection as well as a history of TB are associated with the elevated prevalence of MDR-TB in this setting. Side-effects are common and may impact toward poorer treatment adherence in addition to co-morbidities. Outcomes are favourable in specialised outpatient settings. A decentralised approach reduces the time-to-treatment in other studies, but large-scale implementation is recommended for further evaluation.*

Ethical approval

Full ethical approval was obtained from the Biomedical Research Ethics Committee (BREC), University of KwaZulu- Natal (UKZN) (Reference no. BREC 509/18)

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CHAPTER 1

INTRODUCTION

Tuberculosis (TB) is a systemic disease caused by the bacillus, *mycobacterium tuberculosis* (MTB). It is transmitted via the respiratory route in humans and primarily affects the lungs, although other tissue and organ systems may be involved. Only 10% of affected individuals usually progress to active disease. The global burden of TB has stabilised over recent years at approximately 9 to 11 million new cases in 2019, with South Africa being one of the eight countries that accounts for up to two-thirds of these cases.[1]

The MTB bacillus, in some instances, has evolved and developed resistance to first line drug therapy, most notably, Rifampicin and/or Isoniazid.[2] Multidrug-resistant tuberculosis (MDR-TB), which is defined by resistance to both of these drugs, and isolated Rifampicin-resistant tuberculosis (RR-TB) accounts for almost 500 000 cases each year globally.[1,3] In 2018 and 2019, up to 3.4% of all new TB cases were primary MDR-TB.[1,3]

The development of drug-resistant tuberculosis (DR-TB) is multifactorial. Resistance to first line drugs is due to genomic changes in the MTB, host genetic predisposition, exposure to previous drugs, and co-morbidities like diabetes mellitus.[4] Primary MDR-TB infection (no history of susceptible TB), however, is not uncommon in South Africa, and has been reported more especially in vulnerable population groups such as healthcare workers.[5]

Currently, in KwaZulu-Natal (KZN), in South Africa, the treatment of MDR-TB and RR-TB is co-ordinated from a central site. This was considered to reduce the development of further resistance; however, it may delay the time-to-treatment and patients that reside at a distance from the central site may default follow-up visits due to socio-economic and therefore travel challenges.

1.1 Pathophysiology of Tuberculosis

The initial stage of infection occurs with aerosol transmission of MTB containing droplets from an infected individual. The mycobacteria are then picked up by alveolar macrophages resulting in localised inflammation. The clearance of the infection is determined by the host immune competence and response. Due to cell-mediated immunity, granulomas form, which restrict the spread and multiplication of the mycobacterium, however, this also facilitates disease latency. In the third and final stage, reactivation of the disease may occur.[6]

1.2 Classification of Tuberculosis with Respect to Drug-Susceptibility

There are various classification models used to describe DR-TB, the most common utilised describes the site of infection. The World Health Organisation (WHO) has classified DR-TB for surveillance purposes according to drug-susceptibility patterns namely; RR-TB, MDR-TB and MDR-TB with additional resistance to fluoroquinolones.[1]

The South African classification utilises the confirmatory tests for drug resistance (Table 1-1).

Table 1-1. Classification of TB according to drug susceptibility[7]

CLASSIFICATION	CRITERIA
MONO-RESISTANT TB	Resistance to either Rifampicin or INH
RIFAMPICIN MONO-RESISTANT TB	Resistance to only Rifampicin and not INH
MDR-TB	Resistance to both Rifampicin and INH
PRE-EXTENSIVELY DRUG-RESISTANT TB (PRE-XDR-TB)	Resistance to Rifampicin and INH with additional resistance to either a second-line injectable agent or a fluoroquinolone
EXTENSIVELY DRUG-RESISTANT TB (XDR-TB)	Resistance to INH, Rifampicin and to any fluoroquinolone as well as one or more of the three second-line injectable drugs (Amikacin, Kanamycin or Capreomycin)
PROBABLE RR-TB	Refers to people without bacteriologic confirmation of RR-TB who have symptoms, signs and/or radiology consistent with TB disease and who have been exposed to someone with infectious MDR-TB (>80% concordance between drug-suscept bility test [DST] patterns in probable disease and the likely source patient). These individuals should be treated for RR-TB unless they later have bacteriologic confirmation showing Rifampicin suscept bility.
POSSIBLE RR-TB	Refers to people with TB disease without bacteriologic confirmation of RR-TB who may be at high risk of having RR-TB and who may merit consideration for treatment while awaiting bacteriologic confirmation. These individuals should receive further work up and may be treated for RR-TB on a case-by-case basis even in the absence of bacteriologic confirmation if no other definitive diagnoses can be demonstrated

RR – Rifampicin-resistant; TB – Tuberculosis; INH – Isoniazid *Conradie, F, et al. (Pretoria 2019)*

1.3 Clinical Features of Tuberculosis and Screening

TB has a diverse clinical presentation and typically correlates with the organ system affected. The classical symptoms of cough for at least two weeks, unintentional weight loss, fever and night sweats were initially considered ideal screening tools for TB, but recent studies show that these symptoms may have a lower sensitivity than first reported.[8,9]

A South African study reported that subclinical TB which is defined as having microbiologically confirmed TB in the absence of symptoms, accounted for 23% of all TB cases (n = 28 /124 cases) and 4% of the study population (n = 28/654 participants). These findings support a need for higher sensitivity screening methods in hyperendemic regions.[10]

1.4. Risk Factors for Multidrug-resistant Tuberculosis

There are various risk factors associated with MDR-TB infection with prior exposure to anti-TB drug therapy, as well as HIV co-infection being the most prominent.[11,12] Therefore, a regional risk factor survey has been shown to be appropriate for TB control.[12] HIV co-infection has been associated with higher odds of MDR-TB than HIV non-infected individuals, and is likely due to an increased risk of contracting TB from either reactivation of latent infection, or rapid progression of new infection. Further, HIV co-

infection and TB is associated with younger patients and with higher incidence of extra-pulmonary tuberculosis (EPTB) as well as a higher mortality risk.[12] The largest reported percentage of HIV co-infection and TB is in the African region.[3] Further, associated risk for MDR-TB are lower socio-economic environments and institutional settings.[13,14]

1.5 Diagnosis of Tuberculosis

TB culture is the gold standard for the diagnosis of MDR-TB and sensitivity testing determines resistance and susceptibility patterns. Limitations with MTB culture include inadequacies of sputum collection, storage, and a prolonged finality which may be up to six weeks. [3,15]

The speed and accuracy of diagnosis of MDR-TB has been greatly enhanced by the establishment of molecular testing such as the GeneXpert® (GXP) (83% sensitivity and 98% specificity) and the Xpert MTB/RR ULTRA® which has a higher sensitivity but lower specificity (88% and 96% respectively).[16,17] Molecular testing yields rapid results and potentially allows for earlier initiation of treatment. The assay detects MTB by polymerase chain reaction amplification of the 81-bp fragment of the rpoB gene, and R-R by detection of associated mutations of this region.[18]

Heidebrecht *et al.* studied the role of GXP® in KZN and found it not to be beneficial as a screening tool for TB in comparison to chest radiographs (n = 1/122 with a normal chest radiograph but positive GXP) in a hyperendemic setting. It was found to be valuable in earlier detection of DR-TB (n = 4/44, 9.1%) and as a confirmatory test along with culture (81% sensitivity vs culture).[15]

Sputum sampling has a low yield in EPTB, especially with HIV co-infection, where disease does not affect the lungs. This has led to the need for additional diagnostic tests in these cases. Alere Determine TB LAM Ag assay® which detects the mycobacterial cell wall component lipoarabinomannan (LAM) has re-emerged as a valuable diagnostic test. It has a sensitivity of 56% in diagnosing TB in patients with advanced HIV co-infection specifically in those with CD_4 cell counts of at most 100 cells/mm^3. FujiLAM® is a Japanese origin test and has reported a sensitivity in excess of 70% in detecting TB in these patients.[19]

1.6 Treatment of Multidrug-resistant Tuberculosis

MDR-TB treatment is complex and has been individualised to patient factors and bacteriological sensitivity patterns. Treatment regimens are currently evolving with the development of newer and safer drugs. As with drug susceptible TB, DR-TB treatment is divided into an intensive phase for at least 6 months and a continuation phase which can include up to 18 months of treatment. Five drugs are used in the intensive phase or until sputum smears/cultures are negative.[20] The five usual drugs prescribed in the intensive phase are one of the injectables, Kanamycin or Amikacin; one of the fluoroquinolones, Moxifloxacin or Levofloxacin and Ethionamide, Terizidone and Pyrazinamide.[20]

Within the South African context, Bedaquiline has been made available since 2018 as an alternative to the injectables. Its mechanism of action is by inhibiting mycobacterial adenosine triphosphate synthase and enhances the antibacterial activity of second-line drug combinations.[21,22] Delamanid inhibits mycolic synthesis and has been recommended as treatment for DR-TB under certain provisions, such as in the presence of resistance to fluoroquinolones or injectables and advanced disease. Its safety in pregnancy and/or breastfeeding has not been proven.[23]

Standardisation of treatment for MDR-TB (STREAM) Stage 1 has reported that a shortened nine-month regimen is as effective in patients with isolated drug resistance. Stage 2 involves two short-course Bedaquiline-containing oral regimens that has become an attractive option for MDR-TB treatment and may be utilised more frequently in the future. The American Thoracic Society has since proposed an oral only regimen for treatment, which further recommends against other drugs like Isoniazid, Ethionamide and Pyrazinamide which are considered with high resistance.[24,25]

The latest South African guidelines consists of an injectable-free short-course regimen for nine to eleven months if specific criteria are met or an injectable-free long course regimen for 18 to 20 months.[26]

1.7 Side-Effects and Drug Interactions

Several side-effects to anti-TB treatment (ATT) are expected. The extensive and potentially severe side-effect profile leads to drug intolerance and is a major contributor to patient non-adherence. Further, this results in clinician- guided interruption of treatment.[27,28] (Table 1-2)

Gastrointestinal side-effects are common, but under-reported as they are mild and well-tolerated. Hypothyroidism is a frequent adverse finding among patients on treatment for MDR-TB and results in a large study of more than 6000 patients reported up to 17% of patients affected, most especially in those using p- aminosalicylic acid (PAS) and Ethionamide. Smaller studies also report higher incidences in excess of 50% of cases with hypothyroidism (defined as thyroid stimulating hormone levels > 10mIU/L) during the course of treatment.[29,30]

A South African prospective observational study conducted between 2011 and 2015 reviewed the drug side-effect profile of 206 patients on MDR treatment. More than 90% experienced either clinical or laboratory adverse effects; notably; 72% of patients reported hearing loss; 50% of patients developed peripheral neuropathy, and the most common laboratory abnormalities were hypokalaemia (47%) and abnormal kidney function (46%). No significant difference in side-effect profiles when compared to those patients on concomitant anti-retroviral therapy was demonstrated.[31]

Table 1-2. Common adverse effects of the usually prescribed anti-Tuberculosis drugs

Class / (Drug)	Common Adverse Effects
Aminoglycosides (Kanamycin/Amikacin)	Nephrotoxicity
	Neurotoxicity
	Ototoxicity
Nicotinamide analogue (Pyrazinamide)	GIT symptoms (Nausea, vomiting or diarrhoea)
	Arthralgia
	Hepatotoxicity
Fluoroquinolones (Moxifloxacin/Levofloxacin)	GIT symptoms (Nausea, vomiting or diarrhoea)
	Dizziness
	Anaemia and other cytopaenias
Nicotinamide derivative (Ethionamide)	GIT symptoms (Nausea, vomiting or diarrhoea)
	Hypothyroidism (with PAS)
Cycloserine derivative (Terizidone)	Neurotoxicity
	Cardiac arrythmias
Oxazolidinones (Linezolid)	GIT symptoms (Nausea, vomiting or diarrhoea)
	Dizziness
	Headaches
Diarylquinolines (Bedaquiline)	GIT symptoms (Nausea, vomiting or diarrhoea)
	Arthralgia
	Headaches
	Chest pain
	Prolonged QT intervals
Leprostatics (Clofazimine)	Skin discoloration
	GIT symptoms (Nausea, vomiting or diarrhoea)
	Ichthyosis
	Conjunctival and corneal pigmentation (crystal deposits)
p-aminobenzoic acid analogue (p-aminosalicylic acid)	GIT symptoms (Nausea, vomiting or diarrhoea)
	Neurotoxicity
	Hepatoxicity
	hypothyroidism (In HIV, esp. with Ethionamide)

GIT - Gastrointestinal tract; PAS – p-aminosalicylic acid; HIV – human immunodeficiency virus

1.8 Centralised Versus Decentralised Treatment Approach

Current practice dictates that all patients with suspected or confirmed DR-TB are referred to a central specialised TB centre in Kwa-Zulu Natal. While there is widely accepted benefit of such an approach, concerns over delays in treatment are validly raised. A Durban based KZN study conducted in 2010 reported 75% of referred patients had experienced an average delay to treatment of 12.5 weeks.[32] The study alerted the need for training of staff at peripheral sites and a decentralising care strategy.

Between 2008 and 2010, a prospective study was conducted in KwaZulu-Natal to determine treatment outcomes of a community-based (n = 736 patients) vs centralised (n = 813 patients) treatment approach. The community-based strategy was concluded as superior based on similar treatment success rates (58% vs 54%, p = 0.180), lower default rates (14.5% vs 28.3%, p = 0.004), and a shorter time from diagnosis to treatment (72 days vs 92 days, p < 0.001).[33] A 2017 systematic review and meta-analysis of six cohort studies involving 4026 patients supported these findings by also showing a higher likelihood of treatment success with a decentralised management approach.[34]

1.9 Financial Impact of Drug-Resistant Tuberculosis

A 2012 study reviewed the estimated cost and diagnostic benefit of GXP® vs standard testing. They reported an increase in first-visit diagnosis of TB by 36%, an overall increase in the diagnosis of TB by 30-37% and of DR-TB by 69-71%, however, there was an estimated 55% increase (70 million USD) in the cost of the diagnosis.[35] A subsequent study reported DR-TB as a substantial amount of the total annual TB budget and recommended that a decentralised approach could reduce costs by 26% for each XDR-TB case and 7% of all DR-TB.[36] A KZN prospective study in 2018 involved five different care plans for 1038 patients with MDR-TB which reported the cost per successfully treated patient to be 3 to 4.5 times lower in a community-based model without hospitalisation.[37]

1.10 DR-TB and HIV Co-infection

The increasing numbers of DR-TB and HIV co-infection is concerning. South Africa has the highest TB and HIV co-infection prevalence and one of the highest incidence rates.[38]

Gandhi et al; in 2006, reported the outcomes of patients with XDR-TB and HIV in KwaZulu-Natal. The sample confirmed 44 of 53 patients with XDR-TB to be HIV co-infected. Fifty-two of the 53 patients did not survive. The average survival time from sputum collection to death was 16 days. More than half of the patients (n = 26/47, 55%) had never received ATT previously. The study found no significant change in outcome for age, sex, HIV status or access to anti-retroviral treatment (ART).[39,40]
The psychosocial impact of DR-TB and HIV compounds that of HIV alone, with less structured social support, increased stigmatisation and greater degrees of mental illness being the major subjective complaints from patients in South Africa.[41]

1.11 Rationale for the Current Study

A large emphasis has been placed on the transmission of MDR-TB and XDR-TB in South Africa and especially KwaZulu-Natal, with many studies revealing geographical and genomic evidence for epidemic transmission being a major factor over failure of treatment.[42-44]

This study aimed to report the findings in outpatients diagnosed with DR-TB at a centralised TB hospital in KwaZulu-Natal and hoped to contribute toward an improved understanding of the disease course in the setting of the availability of novel drugs.

CHAPTER 2

METHOD AND STUDY DESIGN

2.1. Literature Review

An extensive literature search was compiled by using an internet website search and online and text journal articles search, using the keywords tuberculosis; Drug-resistant tuberculosis; HIV; and Rifampicin resistance with a focus on local data. Referencing was performed using Endnote X8™ computer programme with searches via Pubmed and Web of Science Core collection.

2.2. Study Design

This is a retrospective, non-interventional and observational study conducted by analysis and audit of patient charts.

2.2.1 Study population

All consecutive patients older than 12 years and newly diagnosed with DR-TB between 1st January 2017 and 31st March 2017 who attended the central TB centre in KZN.

2.2.2. Study location

The study was conducted using the central MDR-TB registry based at King Dinuzulu Hospital in KZN. The centralised registry has data of patients from surrounding regions in the province.

2.2.3. Data collection

Data was extracted from the central DR-TB registry. Patients' laboratory parameters were confirmed using the National Health Laboratory Services Trakcare® online reporting system.
All data was collated and captured onto the data collection tool and electronically stored with password protection (Annexure D).

2.2.4 Study oversight

The study is retrospective and non-interventional in nature and no face-to-face patient contact nor survey was performed. As such, no monitor was required. The study was performed in accordance with recommendations of the Declaration of Helsinki.

2.2.5 Statistical analyses

Descriptive statistics will include mean and 1± standard deviation for quantitative data and frequencies and percentages for categorical data. Depending on the distribution of the data, Chi-square test or Fisher's exact test or the Mann-Whitney test will be applied to analyse categorical data. A two-tailed p-value of less than 0.05 will be considered significant in hypothesis testing and confidence intervals will be reported as 95%. The statistical analyses will be performed with the use of Statistical Package for the Social Sciences (SPSS); version 24, IBM Corp, Armonk, N.Y.USA.

2.3 Ethical Considerations

This study commenced following full ethical approval obtained from the Biomedical Research Ethics Committee, University of KwaZulu-Natal (Reference no. BREC 509/18) and relevant permissions from the KZN Department of Health and hospital management.

The study was conducted in accordance with the National Institutes of Health (NIH) Office of Extramural Research course.

This is a non-interventional study and is retrospective and as such informed consent of each patient was not required, however, the study design and reporting ensured anonymity throughout, and no patient identifiers (individually nor collectively) was published in any way. Consent to access the information was obtained from the head of the establishment and the Provincial Health and Research Ethics Committee. Spreadsheets were electronically stored, and password protected with access granted only to the primary investigator.

CHAPTER 3

DESCRIPTION OF THE SAMPLE POPULATION

3.1 Introduction

In 2018 and 2019, DR-TB had an estimated incidence of half a million cases worldwide. Eight countries are attributable to a large fraction (two-thirds) of these numbers. It stands to reason that the incidence of MDR-TB differs from country to country, region to region, based on observable factors.[1,3]

A United States study conducted between 2011 and 2016 reported 615 (1.4%) TB patients having had MDR-TB. Associated factors in patients with MDR-TB were found to be aged between 15 and 64 years old, a positive contact with a patient with MDR-TB, and a history of TB.[45] In Khayelitsha, a study in 2008 comprising 269 patients within a highly dense population with resource limitations, poorer socio-economic conditions and higher prevalence of HIV co-infection, the reported prevalence of primary MDR-TB was higher (3.3%) and 7.7% in patients with previous TB.[46] Additionally, HIV co-infection is higher in poorer socio-economic environments with HIV prevalence in incidental TB cases in South Africa being 58% in 2019.[1] The province of KwaZulu-Natal in South Africa is divided into 11 municipalities. eThekwini municipality is the predominant epidemiological region of MDR-TB with almost 85% of the disease burden (Figure 3-1). The study site in this study (King Dinuzulu Hospital) is within this region.

In 2005, an outbreak of DR-TB occurred in KZN. Following this outbreak, actions were taken to identify the prevalence of MDR-TB in the province. In 2007, Wallengren et al. found the prevalence of MDR-TB in KZN to be 28 cases/100 000 population and 31 cases/100 000 population in the eThekwini district. Other hyperendemic districts such as Umzinyathi and Umkhanyakude amassed even higher rates of 47 cases and 56 cases per 100 000 population, respectively. Measures to reduce these high prevalence rates were purported to be taken.[47]

3.2 Results

In our study, the total number of MDR-TB patients being treated at King Dinuzulu Hospital between 01/01/2017 and 31/03/2017 was 1371. The population of eThekwini district alone in 2017 was estimated at 3 110 000.[48] The period prevalence of MDR-TB for the above time frame is thus 44 cases/100 000 population. Of these cases, 111 were newly diagnosed with an incidence rate of 3.5 (new) cases/100 000 population. These 111 patients with MDR-TB were included in the analysis which comprised 57 (51.35%) males. Ninety-four (84.7%) patients were from the eThekwini region and most within this region resided in Mayville, Lamontville, Phoenix and Inanda. (Figure 3-1)

eThekwini Municipality

District	n (%)
Mayville and Lamontville	29 (30.85)
Inanda	15 (15.96)
Phoenix	15 (15.96)
Umlazi	14 (14.89)
Tongaat	9 (9.57)
KwaMashu and Ntuzuma	7 (7.45)
kwaDabeka	3 (3.19)
Umbumbulu	2 (2.12)

Figure 3-1: Regional and district representation of DR-TB in KZN

Most patients were of African ethnicity (n = 107, 96.4%) and treated within the state structure (n = 107, 96.4%). Thirty-one (27.9%) patients with MDR-TB did not have HIV co-infection and 11 (13.75%) patients with HIV co-infection were not on ART at the time of MDR-TB diagnosis. The mean CD_4 cell count was 302.7 (±201.9) cells/mm^3 for all patients with HIV co-infection and 54 (67.5%) patients with HIV co-infection had HIV viral counts of less than 1000 copies/mL. The mean duration of ART was 26.57 (±30.48) months. There was no statistically significant difference between males and females in these parameters.

More than one-half of patients (n = 56, 51.5%) had a history of TB and this was significantly higher in males than in females (n = 34, 59.6% and n = 22, 40.7% respectively; *p= 0.046*). Further, males had significantly higher rates of past infections (0.74 (±0.69) vs 0.44 (±0.60) respectively; *p=0.020).* Most sites of MDR-TB affected the pulmonary system (n = 104, 93.7%). Five (4.5%) patients had co-morbidities and no significant gender difference could be demonstrated. Most patients (n = 98, 88.3%) were treated within three months of the time of diagnosis. (Table 3-1)

Table 3-1. Baseline characteristics of sample population

	Male (*n=57)*	**Female *(n=54)***	**Total *(N=111)***	***p-value****
Mean age (*SD*)	32.77 (±9.97)	32.98 (±9.91)	32.87 (±9.90)	*0.912*
Ethnicity				*0.956*
African (%)	55 (96.5)	52 (96.3)	107 (96.4)	
Indian (%)	2 (3.5)	2 (3.7)	4 (3.6)	
Sector (*n, %*)				*0.283*
State	56 (98.2)	51 (94.4)	107 (96.4)	
Private	1 (1.8)	3 (5.6)	4 (3.6)	
HIV status				*0.104*
Negative (%)	20 (35.1)	11 (20.4)	31 (27.9)	
Positive on ART (%)	30 (52.6)	39 (72.2)	69 (62.2)	
Positive not on ART (%)	7 (12.3)	4 (7.4)	11 (9.9)	
Mean CD4 Cell count *(SD)*	305.2 (±225.4)	300.51 (±182.1)	302.7 (±201.9)	*0.918*
VL <1000copies/mL	22 (59.5)	32 (74.4)	54 (67.5)	*0.154*
VL >1000copies/mL	15 (40.5)	11 (25.6)	26 (32.5)	
Mean duration of ART use in months *(SD)*	19.47 (32.44)	32.03 (28.09)	26.57 (30.48)	*0.090*
Previous TB				***0.046***
No	23 (40.4)	32 (59.3)	55 (49.5)	
Yes	34 (59.6)	22 (40.7)	56 (51.5)	
Mean no. of infections (SD)	0.74 (±0.69)	0.44 (±0.60)	0.59 (±0.66)	***0.020***
Site of DR-TB				*0.314*
Pulmonary	54 (94.7)	50 (92.6)	104 (93.7)	
Pleura	0 (0.0)	2 (3.7)	2 (1.8)	
Genito-Urinary	1 (1.8)	0 (0.0)	1 (0.9)	
Lymphatic	1 (1.8)	0 (0.0)	1 (0.9)	
Abdominal	0 (0.0)	1 (1.9)	1 (0.9)	
Meningeal	0 (0.0)	1 (1.9)	1 (0.9)	
Bone	1 (1.8)	0 (0.0)	1 (0.9)	
Co-morbidities				
Renal disease (%)	1 (1.8)	0	1 (0.9)	*0.362*
Hypertension (%)	1 (1.8)	1 (1.9)	2 (1.8)	*0.586*
Diabetes mellitus (%)	1 (1.8)	1 (1.9)	2 (1.8)	*0.586*
Mean time-to-treatment *(Days)*			59 (±79.5)	*0.848*
Less than 3 months	50 (87.7)	48 (88.9)	98 (88.3)	
More than 3 months	7 (12.3)	6 (11.1)	13 (11.7)	

**Chi-square test for categorical data and oneway ANOVA for comparison of means*

3.3 Discussion

Our study sample demonstrates a high number of HIV co-infected patients and many patients with a history of tuberculosis in a predominantly African population group. Most patients with prior TB were male. A local study conducted recently, published treatment success rates of drug sensitive tuberculosis of only 57.38% (n = 342) with 22.32% (n = 133) defaulting follow up and 10.91% (n = 65) being unaccounted for.[49]

A meta-analysis of 16 studies in Ethiopia, which has similar baseline characteristics to our population, revealed that the risk of developing MDR-TB amongst patients with a history of previous TB was 8.1 times higher (95% CI 7.5-8.7) than newly diagnosed cases.[50] This is consistent in our findings, however they reported no significance difference between males and females. Similarly, a Nigerian study reported the highest risk factor for MDR-TB as having a history of exposure to previous anti-TB drugs. They too, did not demonstrate any statistical difference between genders or age.[51] One study found that males have an increased risk of TB and this may infer an increased risk of MDR-TB. There was no greater risk between males and females with a history of previous TB, however as MDR-TB prevalence rises, the risk to males over females rises as well, in some countries.[52] A study performed in 2011 done at King Dinuzulu Hospital reported contrary findings to global trends in that females were far more likely to develop XDR-TB than males and that MDR-TB incidence was rising in females.[53] Although our study looked primarily at MDR-TB cases and not XDR-TB cases, our findings suggest a change in the trajectory predicted by the older study.

Although most patients in our study had pulmonary disease (n = 104, 93.7%), we report seven (6.3%) diagnosed with extra-pulmonary tuberculosis (EPTB). Boonsarngsuk *et al.* found a prevalence of DR-EPTB amongst EPTB of 0.5%, in India which is known to have a similarly high disease burden. The prevalence was also found to be higher in patients with concomitant PTB.[54] An epidemiological study in China reported 33.4% (n = 6433/19279) of TB inpatients had EPTB, of which <0.013% (n = 83) and <0.006% (n = 39) had MDR and XDR-TB respectively. This translated to 10.8% of all MDR cases and 10.8% of all XDR cases reported.[55] Baring in mind the different treatment approaches in these countries, as well as in South Africa, these findings suggest more effort should be made in screening for DR-EPTB, especially amongst MDR and XDR-TB populations. The WHO advises using molecular methods (Xpert® MDR/RR-TB ULTRA®) as first line tests for the diagnosis of EPTB when testing cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid and lymph node biopsy or aspirate ahead of microscopy and/or culture.[56,57]

The most common co-morbidity was HIV co-infection and only 5 (4.5%) patients had diabetes, hypertension, or kidney disease. These findings are consistent with that of Molalign, S. & Wencheko, in their Ethiopian study which reported 17 (5%) of cases with co-morbidities other than HIV.[58] These findings differ from a study in the Philippines, which reported 254 (40%) patients with non-HIV co-morbidities.[59] These differences could be explained by active screening for co-morbidities as well as a low HIV co-infected population in that study. Their study also reported the largest percentage (n = 281, 44%) of patients were between 41 and 65 years of age, which confers a greater risk for diseases of lifestyle.

In one systematic review, the risk of poor treatment outcomes for MDR-TB patients was higher with HIV co-infection or alcohol misuse, but not with diabetes.[60] This review suggests that co-morbidities other than HIV co-infected and alcohol misuse do not play a major role in treatment failure.

Most patients in our study received treatment within three months of diagnosis. A study involving patients from rural Eastern Cape with less favourable socio-economic status than KZN, reported a median delay from sputum collection to diagnosis of 27 days (depending on method) and a further 14 day median delay from diagnosis to treatment..[61] These findings are consistent with our own and suggest that regardless of rural or an urbanised setting, delays in DR-TB are expected. Delays may be explained by the centralised strategy for treatment and the centralised strategy for investigations. Diagnostic modalities play a crucial role in the

overall delay as was described in the Eastern Cape study. Molecular testing in their study, such as the Xpert® MTB/RR ULTRA® was able to greatly reduce time to diagnosis to a single day, as compared to line probe assay (12 days) and culture (45 days). Despite faster diagnostic modalities, time from diagnosis to treatment was unchanged, and this has not been explained. In our study, cases were selected based on date of diagnosis, and time-to-treatment was calculated from this date. Thirteen patients (11.7%) had treatment initiation delays of more than three months, and this comprised more patients with extra-pulmonary disease, in whom making the diagnosis is more difficult. Extra-pulmonary MDR-TB, thus, may represent a shortfall in molecular testing.

Our study draws many similarities to other studies in similar conditions which reinforces the need for further research. A more specific study in XDR-TB may elucidate further on the gender differences. Drug-resistant EPTB requires extensive research on its own and may become clearer as better diagnostic modalities become available. The effect of co-morbidities and treatment delays on outcomes remains unclear and warrants directed studies to define these associations.

CHAPTER 4

DIAGNOSTIC PARAMETERS IN PATIENTS WITH MDR-TB

4.1 Introduction

Microbiological diagnosis of TB is based on positive microscopy, molecular testing and/or culture-based methods.[3] Sputum smear microscopy has limited sensitivity in HIV co-infection.[3,15] Sample cultures remain the gold standard for diagnosis and have the added value of drug-susceptibility testing. An important limitation in culture sampling is the prolonged time to diagnosis.[3] In 2010, the WHO endorsed the molecular and genetic based GeneXpert® test.[3] This nucleic acid amplification test detects both MTB and Rifampicin resistance within two hours.[15] This improved the sensitivity and specificity and has greater accuracy in HIV co-infected individuals compared to routine microscopy.[62] Further, it has been demonstrated to detect MTB in culture negative patients.[62] The more recent Xpert MTB/RIF ULTRA® test improves the sensitivity of the GeneXpert® in HIV co-infection as well as in patients with pauci-bacillary disease.[16] This test has demonstrated lower specificity which may be explained by the presence of dead bacilli or residual MTB DNA either post-treatment or in a latent state.[63] Further, testing has been used to prognosticate outcomes in TB. The 10-year mortality of TB without treatment was estimated at 70% (prior to anti-tuberculosis treatment) and 20% in individuals who were smear-negative (and culture positive).[3] While treatment greatly improves outcomes, it is also greatly dependent on the accuracy of diagnostic modalities.

4.2 Results

GeneXpert® had complete Rifampicin susceptibility results (48 resistant, eight sensitive). Forty (36.0%) patients had inconclusive GeneXpert® results. Only one patient had an inconclusive sputum culture test due to a contaminated sample. Ninety-three (83.8%) patients had positive culture. The mean incubation time to positivity was 17.98 (±10.04) days. We did not demonstrate any significant association with gender and diagnostic testing (Table 4-1).

Table 4-1. Diagnostic microbiology in patients with DR-TB by Gender

	Male (*n=57*)	Female (*n=54*)	Total (*N=111*)	*p-value**
Sputum microscopy				*0.511*
Negative	32 (56.1)	25 (46.3)	57 (51.4)	
1+ Positive	10 (17.5)	16 (29.6)	26 (23.4)	
2+ Positive	7 (12.3)	6 (11.1)	13 (11.7)	
3+ Positive	8 (14.0)	7 (13.0)	15 (13.5)	
Sputum GeneXpert				*0.801*
Negative	6 (10.5)	9 (16.7)	15 (13.5)	
Rifampicin-Resistant	25 (43.9)	23 (42.6)	48 (43.2)	
Rifampicin sensitive	4 (7.0)	4 (7.4)	8 (7.2)	
Inconclusive	22 (38.6)	18 (33.3)	40 (36.0)	
Sputum TB culture				*0.584*
No growth	9 (15.8)	8 (14.8)	17 (15.3)	
Positive	48 (84.2)	45 (83.3)	93 (83.8)	
Contaminated	0 (0.0)	1 (1.9)	1 (0.9)	
Mean incubation time; *Days (SD); n=94*	17 (±9.49)	19 (±10.56)	17.98 (±10.04)	*0.337*

**Chi-square test for categorical variables and oneway ANOVA for continuous data*

All patients had multiple different diagnostic sampling. Less than half of all patients (n = 54, 48.6%) had positive sputum microscopy. Fifteen (13.5%) patients tested negative using GeneXpert® sampling. Fifty-six (58.3%) patients who tested positive on

No significant difference was noted with HIV co-infection and diagnostic modality (Table 4-2).

Table 4-2. Diagnostic microbiology in patients with DR-TB by immune status

	HIV Negative (n=31)	HIV Positive (n=80)	Total *(N=111)*	*p-value**
Sputum microscopy				*0.217*
Negative	13 (41.9)	44 (55.0)	57 (51.4)	
1+ Positive	9 (29.0)	17 (21.3)	26 (23.4)	
2+ Positive	5 (16.1)	8 (10.0)	13 (11.7)	
3+ Positive	4 (12.9)	11 (13.8)	15 (13.5)	
Sputum GeneXpert				*0.112*
Negative	1 (3.2)	14 (17.5)	15 (13.5)	
Positive	16 (51.6)	40 (50.0)	56 (50.5)	
Inconclusive	14 (45.2)	26 (32.5)	40 (36.0)	
Sputum TB culture				*0.816*
No growth	5 (16.1)	12 (15.2)	17 (15.5)	
Positive	26 (83.9)	67 (84.8)	93 (84.5)	
Mean incubation time; *Days (SD); n=94*	16.35 (7.78)	18.60 (10.76)	17.98 (10.04)	*0.332*

**Chi-square test for categorical variables and oneway ANOVA for continuous data*

In the HIV co-infected sub-cohort, patients with CD_4 cell counts of at least 200cells/mm^3 had a higher association with positive sputum microscopy and culture compared to those with CD_4 cell counts less than 200 cells/mm^3. The GeneXpert® yielded higher positivity in patients with lower CD_4 cell counts. The mean incubation time for culture results was comparable and overall, no significant difference was demonstrated based on CD_4 cell counts (Table 4-3).

Table 4-3. Diagnostic microbiology in HIV co-infected patients with DR-TB

	CD4 cell count < 200/mm^3 (n=27)	CD4 cell count ≥ 200/mm^3 (n=53)	Total *(N=80)*	*p-value**
Sputum microscopy				*0.217*
Negative	16 (59.3)	28 (52.8)	44 (55.0)	
Positive	11 (40.7)	25 (47.2)	36 (45.0)	
Sputum GeneXpert				*0.351*
Negative	6 (22.2)	8 (15.1)	14 (17.5)	
Positive	15 (55.6)	25 (47.2)	40 (50)	
Inconclusive	6 (22.2)	20 (37.7)	26 (32.5)	
Sputum TB culture				*0.647*
No growth	5 (18.5)	7 (13.2)	12 (15.0)	
Positive	22 (81.5)	45 (84.9)	67 (83.8)	
Contaminated	0 (0.0)	1 (1.9)	1 (1.3)	
Mean incubation time; *Days (SD)*	18.83 (9.52)	18.49 (11.44)	18.60 (10.7)	*0.904*

**Chi-square test for categorical variables and oneway ANOVA for continuous data*

We compared the findings of the GeneXpert® susceptibility results with the that of the culture results. Twelve (80%) of the 15 GeneXpert® negative samples were confirmed as culture positive and Rifampicin-resistant. Cultures conferred 43 (76.8%) of all GeneXpert® positive tests. Cultures were able to confirm 37 (92.5%) of the 40 inconclusive GeneXpert® tests. A single of the inconclusive GeneXpert® results yielded an inconclusive culture result as well, and two had no traceable culture results.

The total of five GeneXpert® negative or inconclusive results with no result on culture, were treated for extra-pulmonary DR-TB (Table 4-4).

Table 4-4. Rifampicin sensitivity and resistance patterns on GeneXpert compared to culture

	Culture results				
	No result	**Rifampicin sensitive**	**Rifampicin resistant**	**Inconclusive**	**Total**
GeneXpert					
Negative	3 (18.8)	0 (0.0)	12 (13.3)	0 (0.0)	15 (13.5)
Rifampicin-Resistant	11 (68.8)	0 (0.0)	35 (38.9)	2 (66.7)	48 (43.2)
Rifampicin Sensitive	0 (0.0)	0 (0.0)	8 (8.9)	0 (0.0)	8 (7.2)
Inconclusive	2 (12.5)	2 (100)	35 (38.9)	1 (33.3)	40 (36.0)
Total	16	2	90	3	111

We evaluated the results of sputum microscopy and GeneXpert® with that of confirmed culture results (n = 110).

Sputum microscopy yielded a sensitivity of 53.8%, specificity of 76.5% and a PPV of 92.6%. The NPV of microscopy was 23.2% with an AUC of 0.658.

Results from the GeneXpert® test yielded a 78.2% and 14.3% sensitivity and specificity respectively with a PPV of 78.2% and NPV of 13.3%. The AUC of the GeneXpert® was 0.591 (Table 4-5).

Table 4-5. Microscopy and GeneXpert® compared to culture results

	Culture Negative	**Culture Positive**
Sputum Microscopy		
Negative	13 (76.5)	43 (46.2)
Positive	4 (23.5)	50 (53.8)
Total	17	93
GeneXpert		
Negative	2 (14.3)	13 (23.2)
Positive	12 (85.7)	43 (78.2)
Total	14	56

4.3. Discussion

The overall low sensitivity of microscopy in our study is in keeping with a database of systemic reviews, whereas the sensitivity of GXP® appears much lower in smear-negative patients.[17] Another multicentre study did show lower sensitivities (46%) in smear-negative patients for GXP which was improved by with the Xpert® MTB/RR ULTRA® test.[16] This difference can be attributed to the use of GXP in our study population as opposed to Xpert MTB/RR ULTRA® and the testing of drug-sensitive TB in those studies, while our study was exclusively in patients with drug-resistant TB. Another explanation for the low sensitivity of GXP in our study could be in the transit time from sputum collection (sometimes at local clinics) to the laboratory equipped for testing, compromising the sample, however the actual times have not been well documented for this to be confirmed.

Only 35 (72.9%) of the 48 patients with RR-TB by GXP could be confirmed on culture. It is worth noting that all studies determine false positivity on molecular testing by a corresponding negative TB culture, as culture remains the reference standard.[64] GXP specificity for identifying Rifampicin resistance has not been less than 98% in older and recent studies.[16,17,65] This may represent a shortcoming in our microbiological testing especially in cases of high clinical suspicion and high endemicity of disease (high pre-

test probability) where cultures may be false negatives. Local guidelines advise continuing DR-TB treatment in cases with initial Rifampicin resistance on GXP but subsequent sensitivity on line probe assay or culture.[26] Other studies have suggested that possibilities for the discordance in results may be as a result of mixed tuberculosis/non-tuberculosis complexes in the same patient as well as low bacterial loads that are below the threshold for line probe assays, which supports the guideline to continue DR-TB treatment.[66,67] Another study argued that the molecular tests may return as Rifampicin resistance on detection of less significant mutations in the rpoB region that may not necessarily denote resistance.[26,68]

Eight samples from our study revealed a discrepancy between GXP Rifampicin sensitivity and culture Rifampicin resistance. There have been few case reports of patients with drug-sensitive TB that have not responded to routine anti-TB drugs and have shown resistance on culture – suggesting again challenges in the molecular testing method for resistance, where resistant TB strains mutations lie outside the rpoB genomic segment which is used by GeneXpert test to determine resistance.[63]

The findings in our study support that a combination of tests is superior to any single test in diagnosing drug-resistant TB. While Culture remains the gold standard, the molecular tests, when positive, represent a means to faster diagnose patients and therefore reduce the delay to treatment in these cases. Treatment may then be adjusted, as required, once further sensitivities are available.

CHAPTER 5

RESISTANCE AND MUTATION PATTERNS IN MTB

5.1 Introduction

Multiple factors contribute to the development of resistance (where previously susceptible drugs are no longer effective) or mutations. These factors with regards to MTB are: genomic changes, host genetic predisposition, exposure to previous drugs, and co-morbidities like diabetes mellitus.[4]

Data regarding resistance patterns in South Africa are limited despite the high prevalence of disease. In 2013, one study revealed a distribution of <5% resistance to ofloxacin, kanamycin and capreomycin, with XDR-TB comprising around 7% of MDR-TB cases.[26,69] 7.1% of patients screened had MDR-TB in 2016 of which 8% had XDR-TB.[70]

Specific mutations have been recognised and are identified by line probe assays done routinely on all positive TB culture results in KwaZulu-Natal.[26,71] The most common Rifampicin mutation (>95%) is in the rpoB genomic segment and Isoniazid has two main mutations, namely *inhA* and *katG*.[26,71] The inhA mutation denotes low resistance to Isoniazid but high level cross-resistance to Ethionamide, and the katG mutation denotes high level resistance to INH only.[26,71,72]

There are various lineages of DR-TB with the most prevalent in South Africa according to recent research being The Beijing genotype, Latin American and Mediterranean (LAM), East-African-Indian , 'S', 'T' and 'X' clusters.[26,73] The 'S' Cluster currently has the highest prevalence in KZN. The presence of these large clusters lends toward a higher degree of transmission of disease in South Africa and a need for infection control programmes in curbing its spread.[26]

Our study unfortunately does not expand on these lineages, due to a paucity of testing outside of research-driven programmes.

5.2 Results

Most patients in our study had culture-confirmed MDR-TB (n = 55, (49.54%)). 26 (23.42%) patients had Rifampicin only resistance by culture and a further 13 (11.71%) by GeneXpert® with culture negative. Six (5.4%) patients had XDR-TB, 3 (2.70%) patients had Pre-XDR-TB and 3 (2.70%) patients had INH only resistance (Figure 5-1). One (0.90%) patient had mycobacterium other than tuberculosis identified.

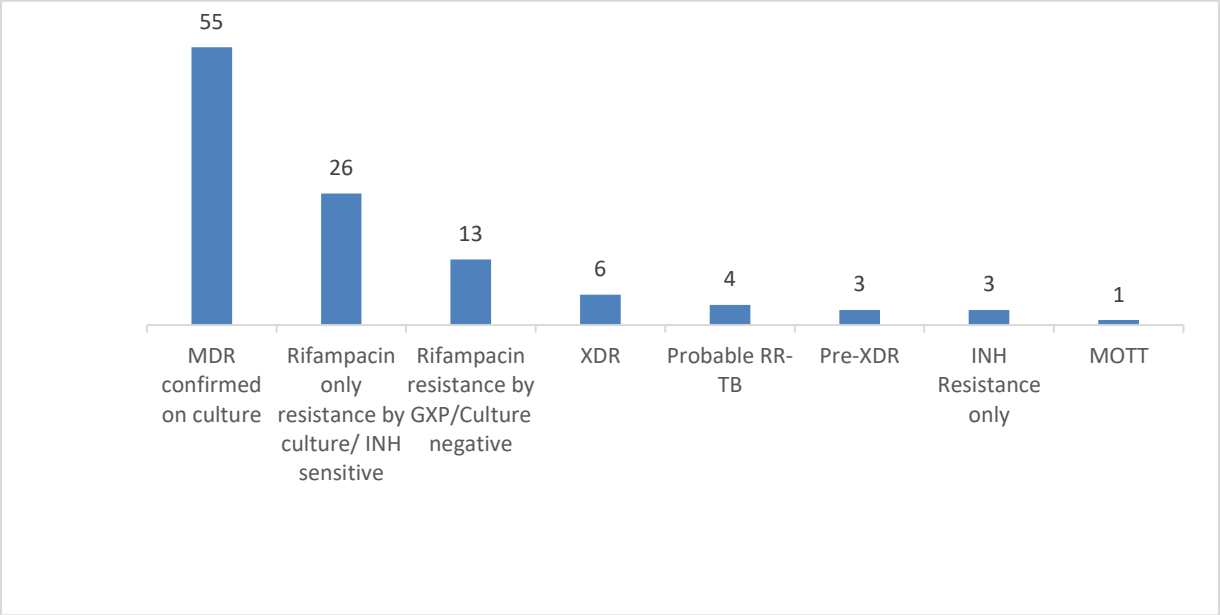


Figure 5-1. Point prevalence of TB Drug resistance

Rifampicin resistance and INH resistance were the most frequent findings among the usual anti-tuberculosis drugs (90 and 65 respectively). Among the aminoglycosides, Streptomycin resistance testing yielded the fewest conclusive results, and Capreomycin and Kanamycin had eight and six resistance results, respectively. Ofloxacin had the highest resistance among the fluoroquinolones (Figure 5-2).

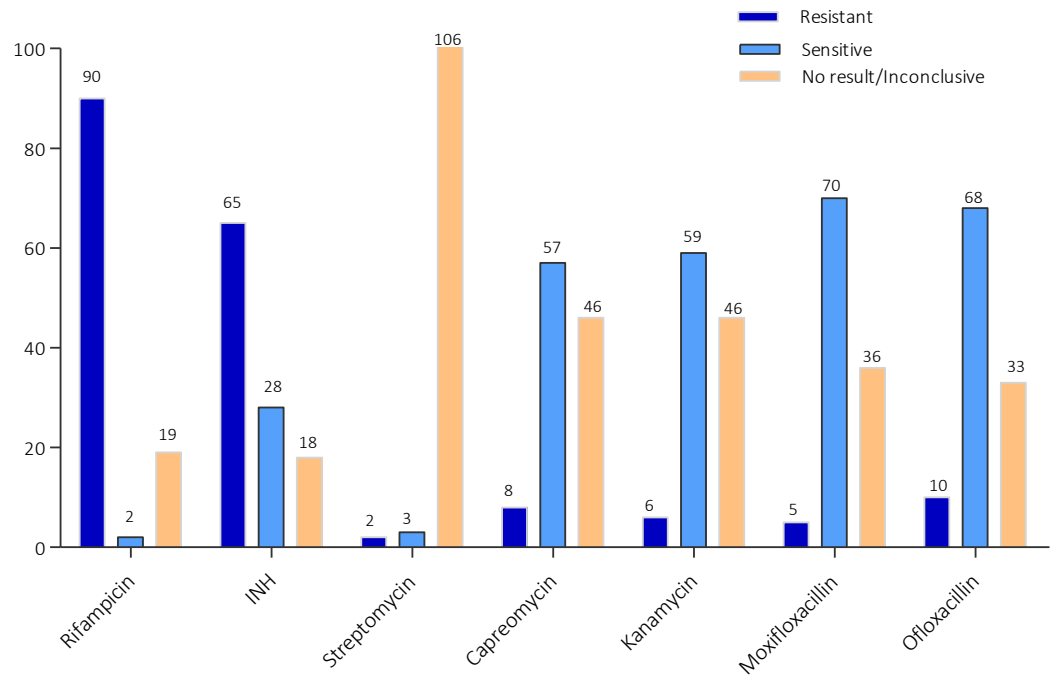


Figure 5-2. Drug resistance patterns on culture

We evaluated resistance patterns in patients with a history of prior TB compared to patients with no prior TB. The pattern of resistance was comparable, and no significant difference could be demonstrated (Figure 5-3).

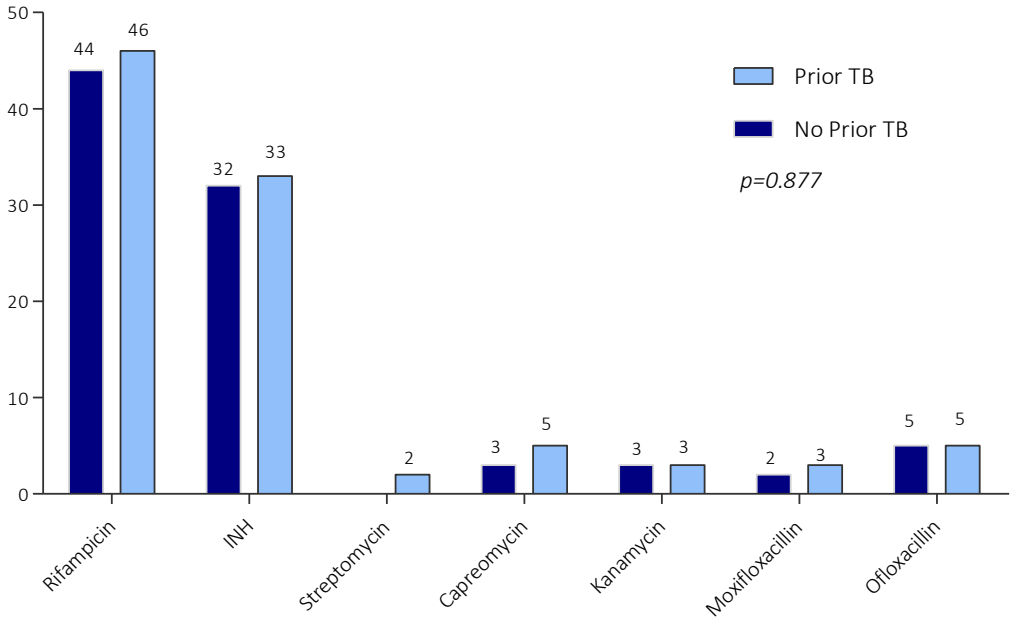


Figure 5-3. Drug resistance between patients with and without a prior history of TB

The most frequent mutations in patients with no prior TB were in katG Mutations and inhA Mutations (n = 54, 48.65% and n = 15, 13.51%) respectively. Of the aminoglycosides, Streptomycin had no detectable mutation and we demonstrated three (2.70%) cases each for Capreomycin and Kanamycin. There was a total of seven (6.31%) fluoroquinolone mutations. We could not demonstrate any significant difference in mutation patterns between patients with a history of TB and those without, *p=0.746*. (Figure 5-4).

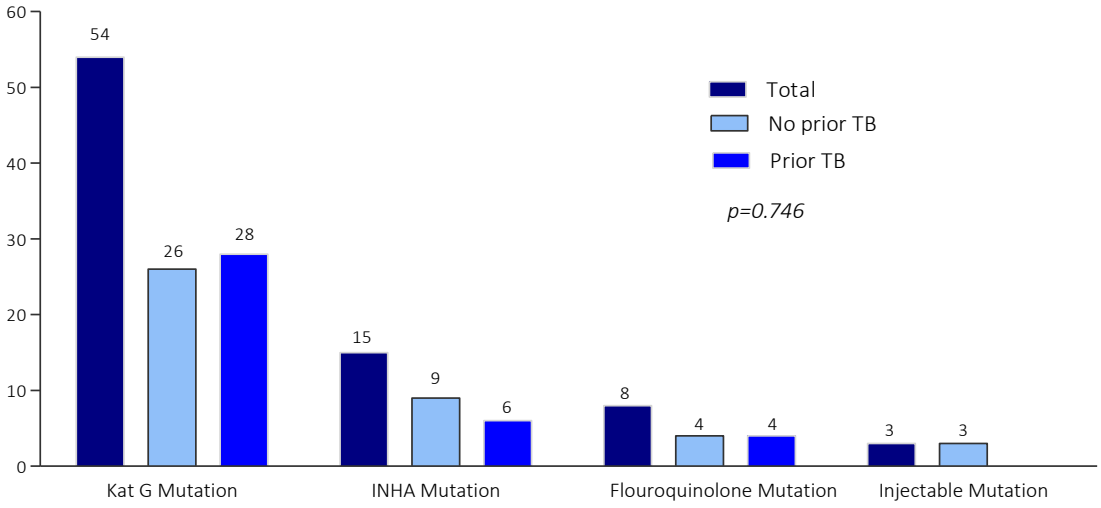


Figure 5-4. Mutations in patients treated for DR-TB

5.3 Discussion

The high level of Rifampicin resistance is expected within the study population given the selection bias and the sensitivity of GXP. Within the patients with INH resistance, the majority had high level resistance with a combination of katG and inhA mutations. Only 5% had an isolated inhA mutation who were treated with high dose Isoniazid. This differs from a previous study done in KwaZulu-Natal that found more than 10% of MDR-TB patients had isolated inhA mutations and would benefit from high dose Isoniazid.[71] This could be explained by progression of resistance and the development of the second mutation, since that study was conducted prior to 2013.

Low percentages of resistance to the fluoroquinolones and injectables can be explained by our study population which is centred around MDR-TB and pre-XDR (with few progressing to XDR-TB). It is also in keeping with the estimated incidence of XDR-TB amongst MDR-TB cases.[26,70]

The lack of significant difference in mutations between patients with a history of previous TB and those without supports previous evidence that primary transmission of resistant bacilli has become the driver of spread of DR-TB.[13,44,73,74]

CHAPTER 6

ANTI-TUBERCULOSIS DRUGS IN PATIENTS WITH DR-TB

6.1. Introduction

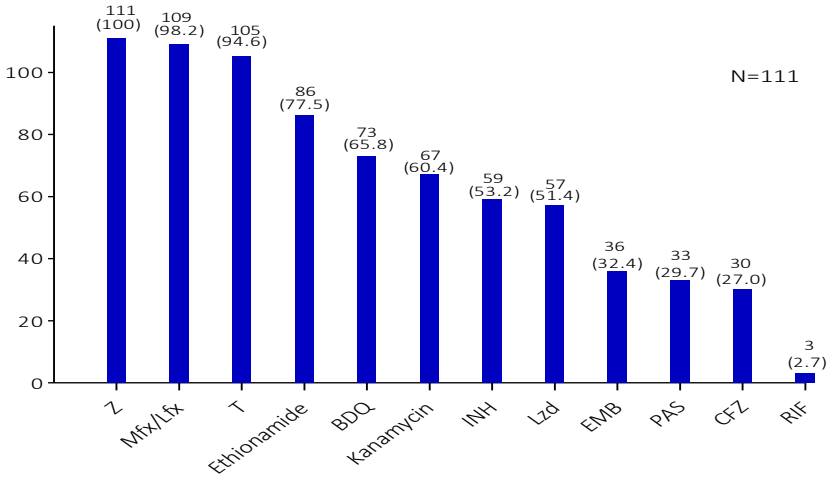
Anti-tuberculosis therapy in patients with DR-TB, in contrast to susceptible TB, extends from at least 9 months up to 20 months.[1] In the past, drug substitutions were made without specific guidelines, leaving many patients on individualised regimens.[1] Currently, in South Africa, patients are still on a combination of regimens, such as short-course injectable-included regimens, short-course non-injectable regimens, and long course regimens with or without injectable drugs.[26] The WHO 2019 guidelines and local 2018 guidelines recommend against the use of injectable agents in both short and long regimens.[2,26]

Side-effects are common, contribute to morbidity, non-adherence, and treatment failure as a result.[30,31,75] Common side-effects to anti-tuberculosis drugs are covered in Chapter 1. (Table 1-2).

The time from diagnosis to treatment remains a challenge limited by the diagnostic method, its accuracy, and socio-economic factors.[32,61]

6.2. Results

The most frequently prescribed drugs in patients with DR-TB were Pyrazinamide (Z), Moxifloxacin or Levofloxacin (Mfx/Lfx) and Terizidone (T); 111 (100%), 109 (98.2) and 105 (94.6%) respectively. Seventy-three (65.8%) patients received Bedaquiline (BDQ). The most frequently prescribed injectable was Kanamycin (n = 67, 60.4%). (Figure 6-1)



Z – Pyrazinamide, Mfx/Lfx – Moxifloxacin/Levofloxacin, T – Terizidone, BDQ – Bedaquiline, INH – Isoniazid, Lzd – Linezolid, EMB – Ethambutol, PAS – p-aminosalicylic acid, CFZ – Clofazimine, RIF – Rifampicin

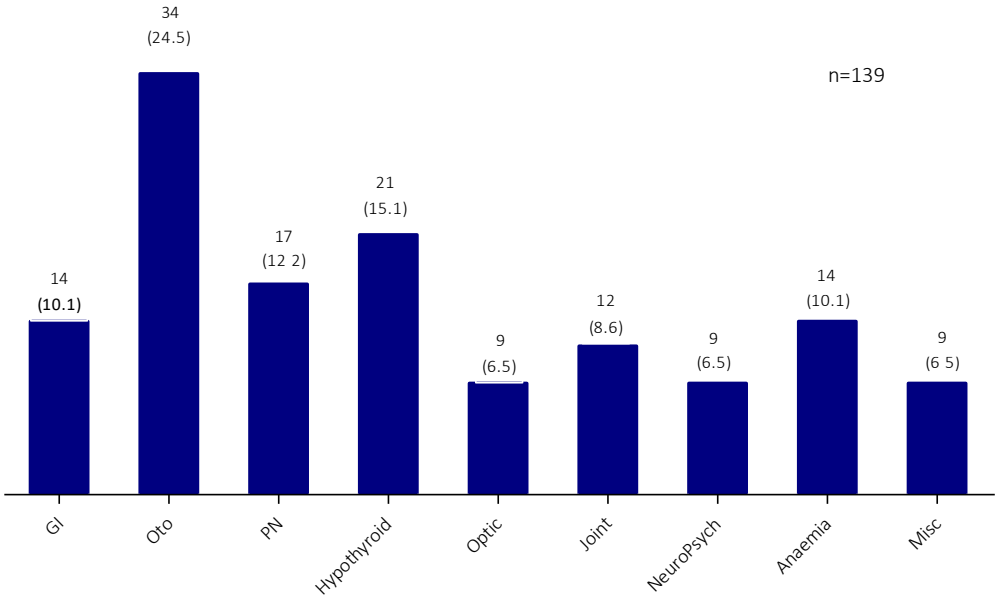
Figure 6-1. Frequency of prescribed drugs in DR-TB

Fifty-one different regimens were prescribed for patients with DR-TB with 6.86 (±1.28) drugs per regimen and 6.92 drugs per patient. The fewest drugs prescribed in a regimen was five and the most in any regimen were ten drugs. The highest number of patients to receive the same regimen was 11 (9.9%) followed by three sets of eight (7.2%) patients with similar regimens. Thirty-five (31.53%) patients had unique TB regimens. (Table 6-1)

Table 6-1. Drug regimens prescribed in patients with DR-TB

No. of different regimens	51
Mean (SD) no. drugs per regimen	6.86 (1.28)
Range of no. of drugs per regimen	5-10
Mean no. of drugs per patient	6.92
No. of patients prescribed Injectables	67 (60.4%)

Thirty-nine (35.14%) patients had no reported side-effects for the duration of their treatment. A total of 139 different side-effects were reported. The most frequent adverse effects were ototoxicity (n = 34, 24.5%) followed by hypothyroidism (n = 21, 15.1%), peripheral neuropathy (n = 17, 12.2%), gastrointestinal symptoms and anaemia (n = 14, 10.1%, each).



GI – Gastrointestinal, Oto – Ototoxicity, PN – peripheral neuropathy, NeuroPsych – Neuorpsychiatric

Figure 6-2. Frequency of side-effects in patients treated for DR-TB

Sixty-three (56.8%) patients were initiated on treatment within six weeks of the confirmed diagnosis. The mean time-to-treatment initiation was 59.32 (±79.55) days (IQR=17.00-70.00). We demonstrated no significant difference in the number of patients treated within six weeks and those beyond six weeks based on the presence of co-morbidities, a history of TB and HIV co-infection. The mean time-to-treatment was however, significantly longer in patients with DR-EPTB compared to patients with pulmonary DR-TB (150.14 (±175.90) days compared to 53.21 (±66.01) days; *p-value=0.002*)

Significantly more patients with a positive GeneXpert® result (n = 35, 89.7%) were treated within six weeks of the diagnosis compared to those with negative results (n = 11, 17.5%); *p=0.013.* The mean time-to-treatment, however, was not significant based on the GeneXpert® result. Microscopy and culture results yielded no significant difference in the time-to-treatment (Table 6-2).

Table 6-2. Time-to-treatment after diagnosis in patients with DR-TB

	Within 6 weeks n (%)	Beyond 6 weeks n (%)	*p-value*	Mean (SD) (Days)	*p-value*
Total population	63 (56.8)	48 (43.2)		59.32 (79.54)	
Gender			*0.893*		*0.799*
Male	32 (50.8)	25 (52.1)		57.44 (67.56)	
Female	31 (49.2)	23 (47.9)		61.31 (91.12)	
Co-morbidities*			*0.658*		*0.118*
Yes	2 (3.2)	2 (4.2)		138.50 (167.87)	
No	60 (95.2)	46 (95.8)		56.66 (74.61)	
Prior tuberculosis			*0.067*		*0.056*
Yes	27 (42.9)	29 (60.4)		73.63 (95.34)	
No	36 (57.1)	19 (39.6)		44.76 (56.60)	
HIV status			*0.304*		*0.581*
Negative	20 (31.7)	11 (22.9)		52.58 (81.40)	
Positive	43 (68.3)	37 (77.1)		61.94 (79.18)	
Site of DR-TB			*0.443*		***0.002***
Pulmonary	60 (95.2)	44 (91.7)		53.21 (66.01)	
Extra-Pulmonary	3 (4.8)	4 (8.3)		150.14 (175.90)	
Microscopy			*0.095*		*0.141*
Positive	35 (55.6)	19 (39.6)		47.89 (65.39)	
Negative	28 (44.4)	29 (60.4)		70.16 (90.21)	
GeneXpert			***0.013***		*0.844*
Positive	35 (89.7)	21 (65.6)		56.61 (88.87)	
Negative	4 (10.3)	11 (34.4)		61.27 (39.96)	
Culture*			*0.500*		*0.906*
Positive	52 (82.5)	41 (87.2)		59.86 (78.69)	
Negative	11 (17.5)	6 (12.8)		57.35 (88.72)	

Chi-square test for categorical data and oneway ANOVA for continuous data

6.3 Discussion

Our study population was largely initiated on the injectable-included regimen. BDQ was also available for specific indications during the study period. It was used during the rollout of the short-course BDQ-lead regimens as well as a substitute when patients developed ototoxicity or nephrotoxicity on the injectable drugs (Kanamycin, etc). These two rationales explain the high exposure of patients to a wide variety of drugs, as well as the high frequency of BDQ use. It can also be inferred that a high degree of ototoxicity encountered on the injectable drugs prompted the switch to BDQ, which supports current guidelines against the use of injectables.

In our study, ototoxicity was the most common side-effect. Ototoxicity is largely underestimated but thought to be prevalent in 41% of people on Kanamycin.[76] In one study, 18.75% (n = 12/64) of patients on injectable drugs developed irreversible hearing loss (re-assessed 1 year later).[77] These findings are consistent with our study group as the majority were also on Kanamycin.

The prevalence of hypothyroidism in our study is consistent with the literature and linked to PAS and Ethionamide.[29,30] The exact mechanism behind the development of hypothyroidism on these drugs is still not known. None of the study patients were initiated on treatment suggesting that none were symptomatic, or signs were subtle and missed.

Peripheral neuropathy is well known side-effect of INH and is prophylactically treated with low dose pyridoxine, occasionally increased to effect.[1] It is noted that a number of patients not on INH still developed peripheral neuropathy in our study. Accumulated cycloserine (Terizidone) levels as well as toxic doses of pyridoxine as possibilities are also linked to peripheral neuropathy.[78] PAS and the aminoglycosides are also known to be Neurotoxic (Table 1-2).

The cause of anaemia is multifactorial and was not investigated in these patients possibly due to mild drops in haemoglobin and correction on treatment. Linezolid is known to affect cell lines, resulting in anaemia or thrombocytopaenia and is also associated with peripheral neuropathy.[79]

In a recent study in Indonesia, which has a high burden of MDR-TB and with a similar DR-TB regimen, Nausea was found to be the most common side-effect, with ototoxicity to a lesser degree.[27] Gastrointestinal side-effects may be associated with many drugs and remains a non-specific finding.

CHAPTER 7

TREATMENT END-POINTS IN PATIENT WITH DR-TB

7.1 Introduction

Treatment success is defined by treatment completion and culture negativity for three consecutive months after the intensive phase.[80] The global successful treatment outcome rate for DR-TB is only 57% as of 2019.[1] Three countries with high disease burden and successful treatment rates > 75% are Kazakhstan, Myanmar and Ethiopia.[1]

Current national guidelines stipulate the intensive phase to be 4 months if culture negative at 4 months and extended to 6 months if culture positive in the short-course (9-11 months) regimen and 6 months (extended to 8 months if culture positive) in the long course (18-20 months) regimen.[26]

Kazakhstan boasts close to 100% treatment coverage with treatment success rates over 80% and in one study showed culture conversion in 89% (195/220) of participants by 6 months.[81] In a retrospective study (2012-2014), Myanmar had a treatment success rate of 80% (1746/2185) and has since then conducted studies on contact tracing/home screening with positive results.[82,83] A meta-analysis between 2003 and 2016 (34 studies) from Ethiopia purported treatment success rates of 83.7%.[84]

Associations with treatment failure in all these studies were linked to HIV co-infection, older age, a history of previous exposure to 2nd line anti-TB drugs, death, and loss to follow-up.

7.2 Results

Fifty-four (48.6%) patients tested positive for TB on sputa sampling, of which, 11 (20.37%) patients still demonstrated positive staining at 6 months and a further 2 (3.7%) patients tested positive at the end of 18 months of treatment yielding a conversion ratio of 74.07%. Ninety-three (83.8%) patients were diagnosed with DR-TB based on a positive culture and two (2.04%) patients had positive cultures at the end of 18 months of treatment (Figure 8).

The remaining 91 patients were culture negative at 18 months and yielded a 97.85% conversion to negative. The mean time to a negative sputum sample was 7.67 (±4.42) months and 5.48 (±6.04) months for a negative culture (Table 7-1).

Table 7-1. Conversion to culture negative

	Baseline	6 months	12 months	18 months	Time to negative (Months)	No. (%) converted to negative
Sputum Auramine; *n (%)*						
Negative	57 (51.4)	100 (90.1)	97 (87.4)	97 (87.4)		
Positive	54 (48.6)	11 (9.9)	14 (12.6)	14 (12.6)	7.67 (±4.42)	40 (74.07)
TB Culture; *n (%)*						
Negative	17 (15.3)	95 (85.6)	93 (83.8)	96 (86.5)		
Positive	93 (83.8)	2 (1.8)	4 (3.6)	2 (1.8)	5.48 (±6.04)	91 (97.85)

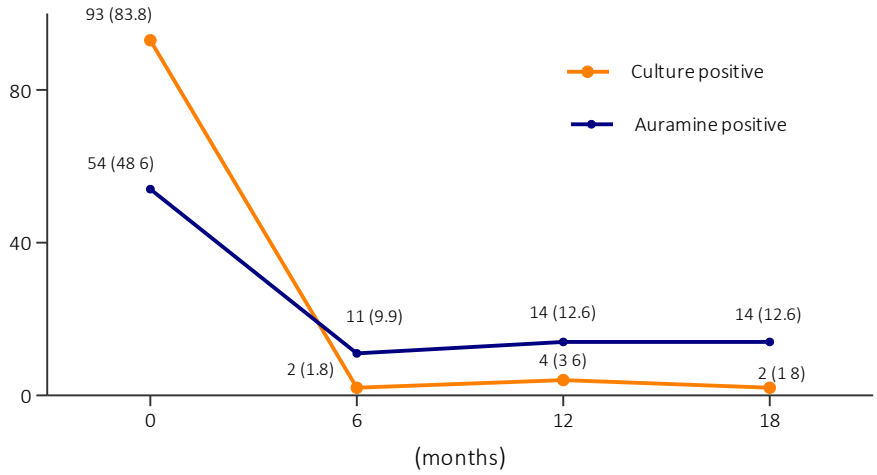


Figure 7-1. Time to auramine stain negative and culture negative in patients treated for DR-TB

Eighty-two (73.87%) patients completed the follow-up until cure. The remaining 29 patients comprised six (5.41%) patients who defaulted follow-up and 23 (20.72%) who were lost to follow-up for undetermined reasons.

7.3 Discussion

Our study reveals a markedly higher positivity rate when comparing baseline sputum culture with sputum microscopy. This is in keeping with previous studies on the sensitivity of these diagnostic tests and the WHO recommendation to utilise both.[1,85,86]

Our results further reveal 85.6% culture conversion by 6 months, with evidence of reversion (from negative to positive culture) in 3.6% at 12 months, and treatment failure of 1.8% at 18 months. The overall treatment success rate was 73.87%, which is lower than Kazakhstan, Myanmar and Ethiopia, but well above the global average (57%) as well the national average of 55%.[26]

The majority of the study population in Kazakhstan received BDQ or Delaminid and almost every patient received Linezolid. Sixty percent were diagnosed with XDR-TB. There was also a higher percentage of co-morbidities such as diabetes mellitus as compared to our population but a markedly lower number of HIV co-infection (only one patient). The Myanmar and Ethiopian studies do report HIV co-infection as an association with treatment failure, and this may explain our lower treatment success rate.

Of concern is the reversion rate after 6 months which may be explained by reduced or less focused follow-up after the intensive phase, poor adherence to lack of counselling or other socio-economic factors. Additionally, our study group underwent centralised care, so a decentralised approach may reveal better outcomes in future studies.[2,32,33,87,88]

Lastly, our treatment coverage is not known from this study, but estimates for 2019, nationally, were less than 75% of the estimated burden of disease[1], and this may contribute to our poor outcomes, as opposed to Kazakhstan, Myanmar and Ethiopia, which show far greater treatment coverage.

CHAPTER 8

STUDY LIMITATIONS AND CONCLUSION

8.1 Study Limitations

Our study was a retrospective chart review and was dependent on the accuracy of documentation in the files and registry. There was no means to follow up on patients who defaulted or to consider the individual socio-economic difficulties. Information was limited only to newly diagnosed, outpatients during the study period under review and therefore did not consider ill patients who may have required admission, which may have had an impact on both true prevalence, and outcomes.

The study was conducted only at a single site; however, King Dinuzulu Hospital is a central, referral institution for MDR-TB and the results may be representative of a larger community.

Finally, all patients with MDR-TB and Pre-XDR-TB were included in the study, even if they later developed XDR-TB, as this was felt to represent outcomes more accurately.

8.2 Conclusion

The increasing incidence of DR-TB annually represents an uncontrolled endemic disease in our setting. HIV co-infection, a history of TB, and a long delay between diagnosis and initiation of treatment remain important influential factors in outcome. Primary transmission of DR-TB is an additional concern. These factors may contribute to the high prevalence of MDR-TB in our study. While GXP and ULTRA are useful tests in combination, it could not demonstrate superiority over culture of TB and drug-susceptibility. Drug adverse effects remain common despite newer drugs and shorter regimens; however, we still demonstrate high inter-individual diversity in treatment regimens. Further review of outcomes in decentralised care would provide more insight into other problems, such as poor treatment compliance and loss to follow up.

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04 September 2019

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Dear Dr Pillay

Protocol: Multidrug resistant Tuberculosis in a hyperndemic setting: A retrospective descriptive study.
Degree: MMed
BREC Ref No: BE509/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 08 August 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 29 August 2019 to BREC letter dated 22 March 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from 04 September 2019. **Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from **04 September 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **08 October 2019.**

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

Supervisor: Vaseng23@gmail.com
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16 July 2020

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Dear Dr Pillay

Protocol: Multidrug resistant Tuberculosis in a hyperndemic setting: A retrospective descriptive study.
Degree: MMed
BREC Ref No: BE509/18

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**04 September 2020**
Expiration of Ethical Approval:	**03 September 2021**

I wish to advise you that your application for recertification received on 12 July 2020 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC).The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 11 August 2020.

Yours sincerely

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
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16 August 2021

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School of Clinical Medicine
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proffjp@gmail.com

Dear Dr Pillay

Protocol: Multidrug resistant Tuberculosis in a hyperndemic setting: A retrospective descriptive study.
Degree: MMed
BREC Ref No: BE509/18

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**04 September 2021**
Expiration of Ethical Approval:	**03 September 2022**

I wish to advise you that your application for recertification received on 30 July 2021 for the above study has be **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC).The start and e dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 14 September 2021.

Yours sincerely

[redacted]

.....
Ms P Pillay
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

16 September 2021

Dr J Pillay (208501921)
School of Clinical Medicine
College of Health Sciences
proffjp@gmail.com

Dear Dr Pillay

Protocol: Multidrug resistant Tuberculosis in a hyperendemic setting: A retrospective descriptive study.
Degree: MMed
BREC Ref No: BE509/18
New Title: Outpatient treatment of Drug-resistant Tuberculosis in a Hyperendemic Setting.

We wish to advise you that your response to BREC letter dated 16 August 2021 has been noted by a subcommittee of the Biomedical Research Ethics Committee. Your application for amendments listed below received on 30 July 2021 for the above study has now been **approved** by a subcommittee of the Biomedical Research Ethics Committee.

Amendments noted and approved:

- Change of title to the above new title.
- Addition of Dr Dhiren Sudhabiriss as co-supervisor.

The committee will be notified of the above approval at its next meeting to be held on 12 October 2021.

Yours sincerely

[redacted]

.....
Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address :75 R.D. Naidu road, Sydenham
Physical Address:PO Dormerton ,4015
Tel: 031 242 6000 Fax: 031 2099586
Email address:shamin_maharaj@kznhealth.gov. za
www.kznhealth.gov.za

DIRECTORATE:
King Dinuzulu Hospital Complex

Enquiries: Dr S.B. Maharaj
Date: 13/02/2019

Dear Dr J. Pillay

RE: PERMISSION TO CONDUCT RESEARCH – MULTIDRUG RESISTANT TUBERCULOSIS IN A HYPERENDEMIC SETTING

I have pleasure in informing you that permission has been granted to you by King Dinuzulu Hospital Complex to conduct research on the Multi-drug Resistant Tuberculosis in a Hyperendemic setting.

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Please note the following:

1. Please ensure that you adhere to all policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure that this office is informed before you commence your research.
4. Neither the District Office nor KDHC will provide any resources for this research.
5. Your attention is drawn to the maintenance of confidentiality with respect to patient's records / files.
6. You will be expected to provide feedback on your findings to KDHC.

Yours sincerely

[redacted]

DR S.B. MAHARAJ
MEDICAL MANAGER

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
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DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_201906_024

Dear Dr J Pillay
UKZN

Approval of research

1. The research proposal titled **'Multi drug resistant Tuberculosis in a hyperendemic setting: A retrospective descriptive study'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at King Dinuzulu Hospital Complex.

2. You are requested to take note of the following:
   a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge

Chairperson, Health Research Committee

Date: 29/08/19

Research Protocol June 2018

First Author: Dr J Pillay, MBChB, MP0765740

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Supervisor: Dr S Gounden, MBChB(Pret) FCP(SA) MMed(Med)

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Multidrug resistant Tuberculosis in a hyperendemic setting: A retrospective descriptive study

Aim
- To determine the prevalence of MDR-TB and surrounding factors at a central TB hospital in the eThekwini district

Specific Aims/Objectives
- Determine the prevalence of MDR TB at King Dinuzulu Hospital from January to March 2017
- Determine the prevalence of MDR TB at King Dinuzulu Hospital from January to March 2012 when testing in the form of Gene Xpert became more available
- Determine the risk factors for MDR-TB, specifically:
    - Number of defaulters
    - Number of patients in whom treatment was withheld and reason behind this
    - Number of re-activation MDR-TB
    - Number of patients with previous susceptible Tuberculosis
    - Number co-infected with HIV
    - The average delay between diagnosis and initiation of treatment
- Determine the treatment outcomes in the same group of patients at 12 months

Background

- The burden of MDR-TB has become a major concern for most health care workers especially in state hospitals. The presence of the untreated disease increases risk of spread to not just inpatients and outpatients, but also to the health care workers themselves. This is exacerbated by any delay to diagnosis and initiation of treatment. While estimates of incidence on an international scale have been documented in numerous articles, no clear correlation has been made with local data and reasons behind the unchecked escalating burden of disease.

Literature Review

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium known as Mycobacterium Tuberculosis. It typically affects the respiratory system but may involve a multitude of systems in the body. When affecting areas other than the lungs (Pulmonary Tuberculosis or PTB), it is referred to as Extra-pulmonary Tuberculosis (EPTB), or denoting the particular area involved (e.g. TB abdomen).

Mycobacterium Tuberculosis is a non-motile rod-shaped obligate aerobe. It is a facultative intra-cellular pathogen and at a molecular level, contains a unique cell wall, a major contributor to its virulence and survival in the host.

The Cell wall is divided into two parts(1):

1. The lower segment or cell wall core (mAGP complex) which comprises of:
    a. Peptidoglycan (PG)
    b. Arabinogalactan (AG)
    c. Mycolic acids (MA)

    d. Long meromycolate and short alpha-chains
2. The upper segment comprises of:
    a. Free fatty acids
    b. Long and short fatty acid chains

    Interspersed with cell wall proteins
    - Phosphatidylinositol mannosides (PIMs)
    - Lipomannan (LM)
    - Lipoarabinomannan (LAM)

Stages of Tuberculosis Infection

The initial stage of infection occurs with aerosol transmission of *mycobacterium tuberculosis* (MTB)-containing droplets from an already infected patient to that of a healthy one. These mycobacteria are then picked up by alveolar macrophages. The multiplication of the mycobacterium results in mild inflammation. The clearance of this infection is determined by weighing the hosts immune-competence against the innate virulence of the MTB strain. Clearance of the MTB is further thwarted by the ability of the mycobacterium to induce an anti-inflammatory response.

- Due to cell-mediated immunity, granulomas form in the next stage. Granulomas restrict the spread and multiplication of the mycobacterium, but also allow for latency of the disease. In the third and final stage, reactivation of the disease occurs.(2)

Clinical presentation

The classical features of TB infection are that of:

- Cough
- Constitutional symptoms (night sweats, loss of appetite and loss of weight)
- Fever
- Other signs and symptoms may appear dependent on the site of TB infection (headaches/meningism in the case of TB meningitis, etc).

Background

Tuberculosis (TB) is the leading cause of death by a single organism worldwide, surpassing that of HIV/AIDs in 2016.(3)

In 2016, the estimated global incidence of TB was 10.4 million, at a rate of 140 cases per 100 000 population.(3) 438 000 cases were estimated in South Africa at a rate of 781 cases per 100 000 population. (3) 298 cases per 100 000 population were noted from Kwa-Zulu Natal.

Treatment of Tuberculosis

Streptomycin was the first drug used successfully in the treatment of TB. Although with initial clearance of the bacillus, recurrence with new drug-resistant bacilli began to emerge. Since 1993, Rifampicin (RIF)/Isoniazid (INH) has been used as part of the short-course first line treatment of TB.

RIF/INH in addition with Ethambutol (ETH) and Pyrazinamide (PZA) forms the intensive phase for 2 months, followed by 4 months continuation phase with just Rifampicin /Isoniazid is largely accepted as standard TB treatment.

RIF is bactericidal working by inhibiting the DNA-dependent RNA polymerase of the susceptible organism, suppressing the initiation of RNA synthesis. INH works against only actively growing organisms by interfering with mycolic acids and disrupting cell walls. Its main side effect is resultant vitamin B6 deficiency necessitating B6

supplementation in patients. ETH also works against the mycobacterial cell wall while PZA is effective against slow growing MTB, by an unknown mechanism.

Multi-Drug Resistant Tuberculosis (MDR-TB)

MDR-TB is defined as at least resistance to both Rifampicin and Isoniazid.(4) Extensively drug-resistant Tuberculosis (XDR-TB) is defined as MDR-TB and resistance to at least one fluoroquinolone and a second-line injectable. (5)

Patients with MDR-TB tend to present in even worse states of health, with poor granuloma formation, high bacterial loads and occasionally, advanced stages of co-infection with HIV.

The Burden of MDR-TB

Globally, there is an estimated incidence of MDR-TB of 450 000 annually. In 2016, there was an incidence of 490 000 and an additional 110 000 Rifampicin Resistant Tuberculosis (R-R TB). (3)

In 2008 there were just about 30 000 cases notified, but this was only an estimated 11% of total cases of MDR-TB. (6)

- 130 120 cases of MDR-TB and R-R TB were notified were notified in 2015.(7)
- 153 119 cases in 2016.(3)

The rising incidence of MDR-TB globally which is more difficult to treat, adds to the mortality rate.(5) Poor therapeutic outcomes in the treatment of standard TB with a resultant increase in resistant strains of the disease remains the main aetiopathogenesis behind MDR-TB.(8)However DOTS (Directly Observed Treatment, short course) showed benefit in the control of Tuberculosis but not in the prevention of resistance development, indicating primary transmission as a major factor in its incidence. (9)

The development of MDR-TB initially thought to be a nosocomial phenomenon now has been attributed to the following causes (10):

- Poor drug availability and non-standardised treatment regimens preceding 1993 – poor adherence and inadequately treated drug-susceptible TB formed the breeding ground for resistance development
- Ongoing standard first-line treatment of either undiagnosed or unrecognised MDR-TB in settings that are resource-scarce – resulting in complete resistance to all first-line drugs
- The transmission of MDR-TB from already infected patients in the community– logical and cyclical rise with rising MDR-TB incidence
- Nosocomial spread as initially presumed – with added higher risk in more susceptible patient groups, such as inpatients especially with HIV

Diagnosis of MDR-TB

The definitive diagnosis of MDR-TB is made on drug susceptibility testing (DST) – of which the traditional method has been through cultures of Tuberculosis then tested against specific anti-TB drugs. This process is time-consuming and operator-dependent (high degree of skill required).

Molecular testing is now establishing itself as the fastest method to diagnose patients, with less skill dependency, less cost, and generally acceptable accuracy. The Gene Xpert (GXP) detects M. tuberculosis and RIF resistance by PCR amplification of the 81-bp fragment of the M. tuberculosis *rpoB* gene and subsequent probing of this region for mutations that are associated with RIF resistance.(11)

GXP being the first line test in most settings in South Africa, including Primary Health Care (PHC) followed by line probe assays – with some clinicians preferring to obtain culture results as well, in certain cases. Largely, resistance demonstrated on GXP is classified as MDR-TB, as resistance to RIF accompanies resistance to INH in greater than 90% of cases. GXP has been shown to be as sensitive to culture in smear-positive Pulmonary Tuberculosis (PTB), with decreasing sensitivity in smear-negative and extra-pulmonary Tuberculosis (EPTB) patient groups.(11)

Risk factors for MDR-TB (10)

- Failure to respond to a first-line DOTS regimen (WHO Category I or II)
- Relapse after a full course of treatment with a first-line regimen
- Treatment after defaulting from treatment with a first-line regimen
- Exposure to a known case of MDR-TB
- Exposure to TB in institutions with high prevalence of MDR-TB, such as a prison or hospital
- Living in areas or countries with high prevalence of MDR-TB
- HIV coinfection

Treatment of MDR-TB

The national standardised treatment regimen for MDR-TB, as per the Department of Health, Republic of South Africa, TB clinical guidelines (2014), is at least 6 months intensive phase with 5 drugs, taken at least 6 times a week, until sputum smears/cultures persistently negative:

- Kanamycin/Amikacin (injectable)
- Moxifloxacin
- Ethionamide
- Terizidone
- Pyrazinamide

The continuation phase excludes the injectable kanamycin/amikacin, also taken at least 6 times a week, for 12-18 months.

Levofloxacin is an alternative to moxifloxacin. Ethambutol may be added as a 6th drug in patients not previously exposed to it for more than a month prior to MDR-TB treatment and in areas with confirmed low prevalence of Ethambutol-resistance. Individualised regimens must be used in patients with previous exposure to any of the 2nd line anti-tuberculosis drugs.(12)

As of June 2018, bedaquiline has been made available to all MDR-TB patients as an alternative to the injectables which have a known high side effect risk. Bedaquiline is a diarylquinoline antibiotic that works by inhibiting mycobacterial ATP synthase. It also enhances the antibacterial activity of second-line drug combinations. Bedaquiline has been previously used primarily for XDR-TB as per WHO guidelines. (13)

Another drug, delamanid has been recommended in addition to standard MDR-TB treatment guidelines under certain provisions.(14)

A short 9-month regimen has shown promise in a study in Bangladesh – known as the STREAM (Standardisation of treatment for MDR-TB) stage 1 – but was only shown to be effective in patients with isolated resistance to both RIF/INH and not to a quinolone. Stage 2 involves 2 short course bedaquiline-containing oral regimens that may hold even greater promise for the future of MDR-TB treatment.(15)

Shortfalls

In Kwa-Zulu Natal, South Africa, there is significant delay in the initiation of treatment for MDR-TB which further contributes to untreated and yet contagious spread of the disease.(16) This is due to MDR-TB treatment only being available and distributed from central points of care.

One study revealed that a decentralised approach to the management of MDR TB showed better outcomes.(17) The difficulty in this approach is that decentralising treatment allows for the abuse or inaccurate prescribing of medications to patients who do not meet criteria, thereby harbouring new resistant strains and ultimately following the failures of standard susceptible TB treatment.

There is a great amount of side effects from the drugs used to treat MDR-TB. Failure to recognise and manage these side effects leads to poor adherence. Side effects range from gastrointestinal, nephrotoxicity, neurotoxicity, ototoxicity, electrolyte wasting and hypothyroidism, amongst others. (10)

Comments

MDR-TB is a disease entity that is establishing itself in modern times almost separate from its base form, that is, susceptible Tuberculosis. Logically, controlling Tuberculosis, should prevent the existence of this entity, however as we can ascertain from the literature, this is a task far easier hypothesised than accomplished.

While attempts made to treat MDR-TB are absolutely necessary, we must not lose sight of the larger goal – the well-rehearsed – "prevention is better than cure". Recognising the risk factors for the development of MDR-TB and addressing them is a key starting point in achieving any favourable outcomes. At the same time, we must be cognisant of the high burden of disease, and the sinister similarities we can expect with XDR-TB as progression from MDR-TB, like MDR-TB from that of susceptible TB.

This study aims to recognise the burden of MDR-TB at a central hospital and the possible contributing factors that will allow us to turn the tide on this debilitating condition.

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16. Narasimooloo R, Ross A. Delay in commencing treatment for MDR TB at a specialised TB treatment centre in KwaZulu-Natal. SAMJ: South African Medical Journal. 2012;102:360-3.
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Key references:

Investigational Plan

- General Schema of Study design
    - Retrospective descriptive study of patients diagnosed with MDR-TB

- Study duration and site
    - Three-month duration from 01/01/2018 to 31/03/2018
    - Single site – King Dinuzulu Hospital – central MDR-TB registry

- Study population
    - All patients with confirmed MDR-TB that appear on MDR registry

- Sampling strategy
    - Patients will be taken directly from the MDR registry with correlation with clinical records and laboratory results

- Statistical planning (variables / confounders)
    - Age
    - Sex
    - Ethnicity
    - Hospital number
    - Means of diagnosis
    - Date of treatment initiation
    - HIV status
    - Co-morbidities

- Sample size
    - To be determined from study duration – approximately 200 patients

- Inclusion Criteria
    - All confirmed cases of MDR-TB older than 12 years and younger than 60 years - total incidence
    - HIV positive and negative
    - Patients with or without Previous Tuberculosis infection, including MDR-TB

- Exclusion Criteria
    - XDR-TB
    - Younger than 12 or older than 60 years
    - Patients with inconclusive results

- Data collection methods and tools
    - Data will be taken directly from MDR-TB registry excluding patients names and transcribed onto the data sheets
    - Hospital numbers will be used to correlate lab specimens confirming MDR-TB and files

- Data analysis techniques
    - All data will be analysed using SPSS software (SPSS 23.0, Armonk NY: IBM Corp). For all statistical comparisons, a 5% level of significance will be used; correspondingly 95% confidence intervals will be used to describe effect size. Medians and inter-quartile ranges will be used for data not amenable to parametric description. Pearson's Chi-square Test or Fishers Exact Test was used to assess the association between categorical variables of interest.

- Statistical analysis
    - Standard descriptive summaries will be used
    - Standard deviations for continuous variables
    - Percentages for categorical variables

Limitations of study

- Data will only be obtained from patients registered at King Dinuzulu Hospital which may underappreciate the actual incidence of MDR-TB or overestimate the change in incidence over time
- Data will only be as reliable as that documented in the registry

Ethical Considerations

- The study will not have any direct or indirect impact on patients appearing in the registry and requires no interaction with any patient
- Patient names will be omitted allowing for anonymity
- The potential benefit from the study will be to re-challenge the clinicians' approach to MDR-TB development
- Expedited approval from BREC will be applied for
- Authorisation from the Hospital manager will be sought in writing

Data Collection Tool

Age ___

Sex Male: __ Female: __

Ethnicity ___

Previous TB Y / N

HIV co-infection Y / N

On Treatment and duration Y ____ / N

CD4 ____ Viral load _____

Other co-morbidities

- Renal impairment ___
- Hpt ___
- DM ___

Date registered

- Treatment initiated > 3 months ___
- Treatment initiated < 3 months ___

Duration of treatment _____

Regimen _____

Side effects _____

Defaulted Y / N

Outcome: _____

Data Collection Tool

Age ___

Sex Male: __ Female: __

Ethnicity ___

Previous TB Y / N

HIV co-infection Y / N

On Treatment and duration Y ____ / N

CD4 ____ Viral load _____

Other co-morbidities

- Renal impairment ___
- Hpt ___
- DM ___

Date registered

- Treatment initiated > 3 months ___
- Treatment initiated < 3 months ___

Duration of treatment _____

Regimen _____

Side effects _____

Defaulted Y / N

Outcome: _____
