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Discordance Between Patient Self-report and Clinician Record of Adverse Drug Reactions to Drug-Resistant Tuberculosis Treatment in Johannesburg, 2015 – 2018.

By

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology in the field of Epidemiology and Biostatistics.

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June, 2022.

DECLARATION

I, Unyime Abasiodiong Iniobong, declare that this research report is my own work. It is being submitted in partial fulfillment of the requirements for the degree of a Master in Science in Epidemiology in the field of Epidemiology and Biostatistics, in the University of Witwatersrand, Johannesburg. It has not been submitted for any degree or examination in any other University.

Signature: 

Date: 28th June, 2022.

DEDICATION

This work is dedicated to the Almighty God, who by him I live, move, and have my very being. By whose grace I can do all things as he strengthens me.

ABSTRACT

Background

Drug-resistant tuberculosis (DR-TB) is a threat to global tuberculosis prevention and control. Treatment is also complicated by adverse drug reactions (ADRs) to the second-line TB drugs. However, there is a lack of data on the discordance between patient self-report and clinician record of ADRs during DR-TB treatment, which may impact treatment outcomes such as adherence or retention in care. This study's objectives were to describe patient self-report and clinician record of ADRs during DR-TB treatment and the degree of the concordance between the two. This study also aimed to determine the relationship between a missed clinician record of ADRs and poor clinic attendance.

Methods

This was a cross-sectional study of adults with laboratory-confirmed rifampicin resistant tuberculosis (TB) on DR-TB treatment at a public-sector outpatient DR-TB clinic in Johannesburg, South Africa between 02/2015–01/2018. The first was a secondary analysis of data that was collected to describe the quality of life and self-reported adverse events among patients on RR-/MDR-TB treatment at Helen Joseph Hospital, Johannesburg, South Africa. The second, a medical record review to collect data on ADRs reported for the patients included in the aforementioned study sample. A descriptive analysis was performed to describe patient self-report and clinician record of ADRs during DR-TB treatment disaggregated by patient demographic and clinical characteristics. To determine the degree of discordance between patient self-report and clinician record of ADRs to DR-TB treatment, Cohen's Kappa statistics (K), Gwet's Agreement coefficient with first order chance correction (ACI) and McNemar tests were used. The relationship between a missed clinician record of any ADRs and the likelihood of missing a clinic appointment (within 3 months of the visit date) was determined using a multivariate logistic regression.

Results

Results from patient self-report of ADRs showed that 38.9% (58/149) reported a total of 122 ADRs while the clinician record of ADRs showed that 67.1% (100/149) reported a total of 141 ADRs. Kappa's scores ranged from -0.01 (poor) to 0.49 (moderate), ACI scores ranged from 0.39 to 0.99, percentage agreement ranged from 62% to 99%. Patient self-report and clinician report were more likely to be discordant when the ADR reported was a sign or

symptom (i.e., rash, vomiting, nausea or joint pain), compared to when the ADR reported was a clinical diagnosis (i.e., hearing loss, peripheral neuropathy, psychosis or anaemia). A missed clinician record of any ADRs was not associated with missing a clinic appointment in 3 months following the visit date. On the contrary, where a clinician missed a record of any ADRs patients appeared less likely to miss their subsequent clinic appointment (51.9 % versus 65.1%; aOR 0.43 95% CI 0.13 – 1.34; p=0.148).

Discussions and Conclusions

The incidence of ADRs obtained from the clinician record was higher than that from patient self-report. Clinician record of ADRs is often objective and based on laboratory results (e.g., haemoglobin for anaemia, alanine transaminase for liver toxicity, or serum creatinine for kidney toxicity) or investigations like audiometry. In contrast, patient self-report of ADR is subjective and based on patient knowledge, understanding, and recall of their experience. Gaps between clinician and patient report of ADRs suggest an opportunity to improve reporting of ADRs by clinicians and improve patient counseling about ADRs related to DR-TB treatment so that patients can recognize ADRs and communicate this information to clinicians during consultations. Improvements in reporting ADRs and appropriate management can result in improved DR-TB treatment outcomes. Early detection, prompt management, and pharmacovigilance reporting of ADRs remain vital factors in managing RR/MDR-TB.

Keywords

Discordance, Adverse drug reactions, Drug-resistant tuberculosis, Multi-drug resistant tuberculosis, Rifampicin resistant tuberculosis, patient self-reports, clinician records.

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NOMENCLATURE / DEFINITIONS/ ABBREVIATIONS:

ACDC	African Union Centre for Disease Control
ACI	Gwet's agreement coefficient with first-order chance correction
ADR	Adverse drug reaction
AE	Adverse events
AIDS	Acquired Immuno Deficiency Syndrome
ALT	Alanine transaminase
ART	Anti-retroviral Therapy
AST	Aspartate transaminase
BDQ	Bedaquiline
BUN	Blood Urea Nitrogen
CD4	Cluster of differentiation 4
CFZ	Clofazimine
DR-TB	Drug resistant tuberculosis
DST	Drug susceptibility test
EPTB	Extra pulmonary tuberculosis
EDRweb	Electronic Drug-Resistant Tuberculosis Register
GGT	Gammaglutamyl transferase
g/dl	Grams per deciliter
Hb:	Hemoglobin
HHIE-S	Hearing Handicap Inventory for the Elderly Screening Version
HIV	Human Immunodeficiency Virus
HRQOL	Health related quality of life
K	Cohen kappa's statistics
Kg	Kilograms
ID	Identification number
INH	Isoniazid
IQR	Interquartile range
IU/I	International unit per liter
LFX	Levofloxacin
LPA	Line probe assay
LTFU	Loss to follow up
LZD	Linezolid

MCC	Medicines Control Council
MDR-TB	Multidrug resistant tuberculosis
mg/dl	Milligrams per deciliter
MTB	Mycobacterium tuberculosis
mU/l	Milliunits per liter
NDoH	National Department of Health
NHLS	National Health Laboratory Services
NPC	National Pharmacovigilance Centre
aOR	Adjusted Odds Ratio
cOR	Crude Odds Ratio
OR	Odds ratio
PHC	Primary health care clinic
PTB	Pulmonary tuberculosis
REDCap	Research Electronic Data Capture
RIF	Rifampicin
RR-TB	Rifampicin resistant tuberculosis
SADR	Severe adverse drug reaction
SD	Standard deviation
SF-36	Medical outcomes short form - 36
TB	Tuberculosis
TBFP	Tuberculosis focal point
TDR-TB	Total drug resistant tuberculosis
TRD	Terizidone
TSH	Thyroid stimulating hormone
USA	United States of America
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis

CHAPTER 1

1.0 Introduction

This chapter gives a general overview of the burden of tuberculosis (TB) and rifampicin-resistant (RR-) tuberculosis and multi-drug resistant (MDR-TB), as well as the rationale for the study and ends with an explicit review of relevant literature on the topic. It also describes the aims and objectives of the study.

1.1 Background

Tuberculosis (TB) is a public health issue globally. It is caused by Mycobacterium tuberculosis, bacteria that mostly affects the lungs. Current estimates shows that a quarter of the world population is infected by TB and most of these cases are found in low- and middle-income countries[1]. Approximately 50% of the world cases of TB are found in 8 countries: Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines and South Africa.[2] Every year, 10 million people are infected with TB bacteria but are not ill with the disease hence cannot transmit the disease. In 2019, the World Health Organization (WHO) estimated that 7.1 million people with TB were newly diagnosed and notified, increasing from 7.0 million in 2018, 6.4 million in 2017 and 5.7-5.8 million yearly between 2009-2012.[1]

In 2019, WHO estimated 465,000 new cases and 182,000 deaths caused by RR/MDR-TB globally.[1] RR-TB can be defined as TB that is resistant to rifampicin whereas MDR-TB is TB that is resistant to at least rifampicin and isoniazid (INH) with or without resistance to other first-line drugs used in the treatment of tuberculosis. Among the new cases of TB, 4.1% have RR/MDR-TB, and 19% of these people have been previously treated for TB.

TB is a major public health concern in South Africa. In 2018, it was estimated that 301,000 South Africans had TB, at a rate of 520 per 100,000 with 63,000 deaths.[2] TB continues to be the leading cause of mortality in HIV positive people.[2] Similarly, the increasing number of people with HIV infection in South Africa continuously drives active TB disease, with estimates showing that 42,000 of the 63,000 deaths in 2018 from TB were HIV positive.[2] In 2019, South Africa was reported to have the highest number of patients with MDR-TB in Africa, with an estimate of 23 out of every 100,000 people being infected with RR/MDR-TB.[1]

According to the WHO, "*Adverse drug reactions (ADRs) are defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function*".[3] Drugs used to treat RR/MDR-TB have many known ADRs ranging from those that temporarily reduce quality of life (e.g. abdominal pain, rash, nausea, vomiting) to those that cause long-term disability (e.g. irreversible hearing loss) or are potentially life threatening (e.g. renal failure, psychosis, seizures) and may be common in patients receiving treatment for RR/MDR-TB.[4,5] Second-line drugs are usually expensive and have recognized toxicities from the doses and durations required to treat RR/MDR-TB. Some of these toxicities require hospitalization to manage their effects and other associated complications.[4]

RR/MDR-TB treatment aims to achieve a favorable treatment outcome such as cure or the completion of treatment in the absence of a microbiological confirmation. ADRs can lead to the clinician or patient interrupting, discontinuing, or reducing the dosage of treatment before completion, resulting in unfavorable treatment outcomes such as increasing the risk of loss to follow-up, treatment failure, or even death.[6] There is a lack of data on the discordance between patient self-report and clinician record of ADRs during drug-resistant (DR-) TB treatment, which may impact treatment outcomes such as adherence or retention in care. Early identification and prompt management of ADRs can result in better treatment outcomes. In 2015, the National Department of Health (NDoH) in South Africa provided guidelines for reporting ADRs. Patient management of ADRs is monitored and adjusted to suit the contributions from provincial expert clinical sub-committees.[8] ADRs are to be recorded and captured in the electronic drug-resistant TB register (EDRweb), which in turn is then reported to the South African Health Products Regulatory Authority (SAHPRA). Before reporting through EDRweb, the attending clinician submits to the National Pharmacovigilance Centre (NPC) and the manufacturer following the guidelines provided during training for each new drug. Common problems associated with clinician reporting of ADRs are heavy clinical workload, insufficient time to fill in the records, inadequate knowledge of the pharmacovigilance system in the hospital, unconfirmed ADRs diagnosis, and conflict in the reporting of ADRs.[9]

1.2 Literature Review

1.2.1 The burden of TB

Tuberculosis (TB) is a disease that mainly affects the lungs caused by an organism called Mycobacterium tuberculosis (MTB) presenting as an active or latent disease.[7] People with TB infection can be classified as either having latent tuberculosis infection (LTBI), this is an asymptomatic clinical state that cannot be transmitted, or an active TB disease characterized by the presence of clinical symptoms from the infection.[8] TB bacteria are spread through the air from one person to another. The TB bacteria are dispersed into the air when a person with TB disease of the lungs or throat coughs, speaks or sings. People nearby may breathe in these bacteria and become infected. TB that affect the lungs is pulmonary TB (PTB) while TB that affect other parts of the body including lymph nodes, gastro-intestinal tract, viscera, kidneys, bones and even the central nervous system is extra pulmonary tuberculosis (EPTB).[9]

TB can be classified based on its response to drug sensitivity into drug sensitive TB or DR-TB. MDR-TB is defined as DR-TB that is resistant to at least rifampicin (RIF) and isoniazid (INH) which are the most effective first-line drugs for the treatment of TB.[10] RR-TB, is TB that is resistant to rifampicin with unidentified or awaiting sensitivities to additional drugs, rifampicin mono-resistant TB is TB that is sensitive to isoniazid while extensively drug resistant (XDR) TB is MDR-TB with additional resistance to second-line drugs of the fluoroquinolones and at least one of the aminoglycosides (which are injectables) or cyclic peptide classes, and pre-XDR TB is defined as MDR-TB with resistance to either a fluoroquinolone or a second-line injectable drug but not against both of these drugs simultaneouesly.[11,12]

TB is a threat globally; it is one of the top 10 causes of death worldwide and the foremost sole infectious agent after human immunodeficiency viruses (HIV) / acquired immunodeficiency syndrome (AIDS). TB and HIV co-infection is also a global health problem causing immune suppression and the most shared cause of death among HIV positive people.[13] WHO reported about half a million people developed RR-TB worldwide in 2019, with 78% of them having MDR-TB.[1]

Globally, it is reported that 1.1 million people are living in with HIV/TB co-infection with 80% of them living in sub-Saharan African countries.[14,15] In 2019, TB had caused 1.2 million

deaths in HIV negative people and 208,000 deaths in HIV positive people.[2] South Africa still remains one of the countries mostly affected by HIV/TB co-infection thus bearing the impact of the greatest crisis of TB worldwide.[16] Globally, in 2019, almost half a million people had rifampicin-resistant TB (RR-TB) of which 78% had multi-drug -resistant (MDR-TB).[1]

South Africa is counted as one of the countries with about 80% of the world's estimated cases of MDR-TB. [9] MDR-TB and HIV co-infection has been reported as a 'Twin Epidemic' and this epidemic is primarily driven by HIV infection and the lack of airborne infection prevention measures. The rapid spread of MDR-TB among HIV patients is due to altered immunity to fight the MDR-TB bacteria, this increases the chance of developing TB among HIV infected people to 29% compared to HIV uninfected people.[17] South Africa TB incidence is high, but has been declining since the roll-out of ART though with a mounting widespread of multidrug resistant (MDR-TB) and extensively drug resistant (XDR) TB.[18] In 2018, it was reported that 3.5% of the new cases with 18% of formerly treated TB cases have multidrug resistant (MDR-) TB. Although the overall TB incidence is falling in response to increasing antiretroviral (ART) coverage, the incidence of drug-resistant (DR) TB is increasing, making rifampicin resistant (RR-) and MDR-TB a public health concern. RR/MDR-TB threatens to overturn decades of progress on TB control.[19] The exact burden of RR/MDR-TB in Africa is unclear with only 51% of countries having complete survey data.[19] Due to this insufficient data, modelling estimates reported 92,629 cases of RR/MDR-TB in Africa with Nigeria and South Africa accounting for 42% of the burden.[19] South Africa is the ninth country with the highest number of new cases of DR-TB worldwide, with an estimated number of 23 out of every 100,00 people being infected with RR/MDR-TB.[10] A meta-analysis conducted in 2017 showed a pooled prevalence of RR/MDR-TB with highest in Southern African and lowest in Eastern African countries, this finding did not come as a surprise as South Africa contributes substantially to the regional and global burden of TB,[10] thus giving the Southern African region the highest prevalence of 3.1% (2.1 – 4.2) of RR/MDR-TB.[19]

1.2.2 Diagnosis and treatment of drug-resistant TB

The diagnosis of RR/MDR-TB has been greatly limited by the lack of affordable and effective rapid diagnostic methods for drug sensitivity. Many methods including phenotypic and molecular methods are being explored to establish accurate, reliable and rapid methods

which can be assessed and used in high burden areas such as South Africa.[20] Culture methods using drug sensitivity procedures take a long time to identify drug resistant microbes on solid media. This, however, is the most sensitive method and culture-based drug susceptibility testing (DST) is considered the gold standard.[20] Liquid based culture methods are more sensitive than the solid media cultures which give a significantly higher yield and reduces the turnaround time though has a higher cost which is an issue in low resource settings. Rapid phenotypic methods have been adopted for the speedy detection of RR/MDR-TB with even less turnaround time, this method may be more cost-effective but it is difficult to perform and there is limited knowledge on the field performance in developing countries.[21] Rapid molecular methods can also be used as this is used to identify the specific mutations responsible for drug resistance.[21] Line probe assay (LPA) is a rapid molecular test which can identify the TB bacilli and drug resistance. Though more complex technically, and takes longer time to carry out than Xpert MTB/RIF assay, it has the capacity to detect isoniazid and rifampicin resistance, unlike Xpert MTB/RIF.[22] In 2011, South Africa enhanced its capacity to test for RR/MDR-TB by introducing Xpert MTB/RIF (Cepheid), a molecular test which identifies both TB and rifampicin resistance within 2 hours.[23,24] This has helped improve treatment capacity, reduce treatment delays and enhance patients' outcomes.

Initiation of treatment for RR/MDR-TB requires assessments of previous treatment history and careful laboratory investigations for drug sensitivity.[25] The proposed treatment regimen for RR/MDR-TB includes a minimum mixture of four drugs which are chosen by a stepwise selection process among five sets based on effectiveness, safety and price. From the first group (which are the first-line oral drugs) high doses of isoniazid, pyrazinamide, then ethambutol. The second group are the fluoroquinolones with the first choice being high dose levofloxacin. The third group are the injectables recommended be used in the order capreomycin, kanamycin, then amikacin. The fourth group, called the second-line drugs are recommended to use in this order thioamides, cycloserine, then aminosalicylic acid. The fifth group are drugs that are argued not very active or which have scarce clinical data on them and are recommended to be used in this order, they include clofazimine, amoxicillin with clavulanate, linezolid, carbapenems, thioacetazone, then clarithromycin.[26]

Before 2016, the standard long-course regimen for RR/MDR-TB treatment was 18-24 months long with daily injections with aminoglycoside for the first 6 months. However, this regimen had numerous ADRs leading to poor retention, treatment failure, loss to follow-up

(LTFU), poor treatment outcomes and increasing risk of death in these patients.[27–29] With encouraging results from studies using 12 months regimens or less, in 2016 WHO approved a short aminoglycoside containing treatment regimen of 9-12 months. In 2018, the South African National Department of Health (NDoH) decided to include Bedaquiline (BDQ) routinely into RR/MDR-TB treatment thus making South Africa the first country to begin the injection free oral short course regimen of BDQ and linezolid for 9-12 months. This new regimen is said to have the potential of eliminating hearing loss as an ADR resulting in reduced deaths, reduced loss to follow up and improve treatment outcomes.[27–29] To improve treatment capacity, reduce delays and improve patient's overall outcome, the South African National TB control program, put forward a framework for the "decentralized and deinstitutionalized management" to RR/MDR-TB, approving outpatient treatment at sites nearer to their homes while remaining resident at home all through the treatment rather than in facilities.[29,30] There were several RR/MDR-TB treatment regimen and diagnostic guidelines in effect over the course of this study. These have well described previously in the HRQOL study.[31]

1.2.3 Adverse drug reactions (ADRs) to RR/MDR-TB treatment

Drugs used to treat RR/MDR-TB have many known ADRs and these ADRs are very common in patients receiving this treatment.[4] Second-line drugs are usually expensive and have recognized toxicities from the doses and durations required to treat RR/MDR-TB. Some of these toxicities require hospitalization to manage their effects and other associated complications.[4] Some ADRs can be confirmed by laboratory tests if at least 1 laboratory value is abnormal. For ADRs not defined by laboratory tests, patients self-reports and clinicians reports are used to classify ADRs.[32]

Data on worldwide prevalence of ADRs to RR/MDR-TB are limited, the prevalence of ADRs reported from various studies across the world ranged from 69% to 96%.[7,33] The reasons for these differences across studies may be connected with various factors which include different definitions of ADRs terms by physicians, whether the ADRs was subjective (reported by the patient) or objective (recorded by the clinician) from the results of laboratory tests, associated co-morbidities like diabetes, differences in the use of various anti-RR/MDR-TB drugs and HIV co-infection.[4,7,32,33] A study done at China in 2017, reported that 90.7% of patients developed as least one type of ADRs during RR/MDR-TB treatment and about half

of the patients required a change in RR/MDR-TB treatment, and most occurred during the first 6 months of treatment. Previous studies done have reported higher frequencies of ADRs to RR/MDR-TB in patients who were coinfected with HIV compared to those who were not.[34,35] The incidence of arthralgia and gastrointestinal symptoms was reported to have the highest frequencies of ADRs to RR/MDR-TB treatment.[32] A systematic and meta-analysis were done in 2012, found that 57.3% of patients had experienced at least one ADR ranging from mild, moderate and severe.[36] ADRs can lead to clinician or patient interrupting, discontinuing or reducing the dosage of treatment before completion which may increase the risk of , lost to follow up, treatment failure or even death.[6]

1.2.3.1 ADRs reported in patients with RR/MDR-TB

Common examples of ADRs to RR/MDR-TB treatment include ototoxicity, vision loss, anorexia, insomnia, peripheral neuropathy, arthralgia, skin itching and rashes, depression, nephrotoxicity, gastrointestinal disturbances, nausea and vomiting, psychiatric disturbances, hepatotoxicity and nephrotoxicity etc.[4,31] ADRs reported by patients on RR/MDR-TB treatment are related to the drug regimen used. The aminoglycosides like kanamycin, streptomycin, capreomycin and amikacin are commonly associated with ototoxicity, hearing loss, gastrointestinal disturbances, nephrotoxicity, hypokalemia, peripheral neuropathy and hepatotoxicity. Pyrazinamide commonly causes arthralgia, gout and hepatitis. Para-aminosalicyclic acid frequently causes hepatitis and gastrointestinal disturbances. Cyclocerine is frequently associated with psychiatric disturbances and depression.[37,38]

1.2.3.2 Risk factors for ADRs to RR/MDR-TB treatment

Several factors have been identified to be associated with the likelihood of development of an ADR. The risk of development of these ADRs may be dependent on patients' characteristics and also on associated events occurring during the duration of treatment, which could determine adherence and successful treatment outcomes.[39] These factors include age: very young or old age, while young people may not metabolize and eliminate drugs efficiently, older people may have other health issues and taking drugs that may react with or worsen the ADRs to RR/MDR-TB treatment. Also, as people age, the liver functionality decreases and is less able to metabolize and the kidney excretes drugs from the body. Concomitant use of other drugs is also a factor that affects the metabolism and excretion of drugs just like older age and the number and severity of ADRs rises unduly as the number of drugs increases. The

use of alcohol, which is technically a drug may cause liver damage further increasing the risk of ADRs. Smoking may cause reactions to the drugs hence increasing the risk of ADRs.[39,40] Sex as a risk factor for developing ADRs is an important factor determining drug use and reactions, females are reported to have a greater risk of ADRs compared to males. In fact, older age and females are significantly associated with ADRs leading to hospitalizations.[40] Inherited factors can make some people more prone to the toxic effects of certain drugs and certain diseases can alter absorption, metabolism, elimination and response to drugs.[40] Other factors are overweight/obesity, pregnancy, breastfeeding, anaemia, underweight, malnutrition, diabetes mellitus, HIV infection and hepatitis B or C co-infection.[39–41]

1.2.3.3 Classification of ADRs

ADRs can be reported by patients (subjective) or reported by clinicians/ doctors (objective) based on the results of laboratory investigations. Examples of ADRs commonly reported by patients are nausea, vomiting, abdominal pains, headaches, diarrhoea, myalgia, joint pain, arthralgia etc. Examples of ADRs commonly reported by clinicians/doctors are renal dysfunction, anaemia, hypothyroidism, hyperthyroidism etc.[33] Renal dysfunction is monitored using the glomerular filtration rate (GFR) using the Cock Croft Gault formular. This is graded as mild, moderate and severe renal dysfunction. For mild, GFR of 60 – 89 millilitre per minute per 1.73m^2 (ml/min/1.73m^2) with evidence of kidney damage. Moderate, GFR of 30 to 59 ml/min/1.73m^{2}and severe is GFR of 15 – 29 ml/min/1.73m^2 or requiring dialysis.[42] According to WHO, anaemia levels is categorized based on the Hb, sex and pregnancy status. Normal haemoglobin (Hb) is ≥12 grams per decilitre (g/dl) for females not pregnant and Hb ≥13g/dl for males while mild anaemia is defined as a Hb between 11 – 11.9 g/dl for females not pregnant and 11 – 12.9 g/dl for males. Moderate anaemia is defined as a Hb between 8 – 10.9 g/dl and severe anaemia a Hb less than 8 g/dl. Normal thyroid stimulating hormone (TSH) ranges between 0.4 – 4.0 milliunits per litre (mU/l), hyperthyroidism is when the TSH is between 0-0.4 mU/l and hypothyroidism occurs when the TSH levels are ≥10 mU/l.[43]

The severity of ADRs is not always associated with the frequency and duration of treatment or the resistance pattern of treatment. There is no standardized grading for the severity of ADRs, however, some studies have classified ADRs into three grades as follows [35,37,44]; Grade 1 are mild, Grade 2 – moderate and Grade 3 – severe. For mild ADRs no medical

intervention is required, moderate ADRs required little or palliative/ adjunct intervention and severe adverse drug reactions (SADRs) required hospitalization, change in treatment regimen or total discontinuation of treatment. Practical and watchful management of SADRs in patients on treatment for RR/MDR-TB especially in those co-infected with HIV or taking other drugs is required. [35,37,44] Most severe ADRs were reported to occur in the intensive phase while the mild ADRs was said to occur more frequently in the continuation phase of the treatment.[45]

1.2.3.4 Management of ADRs to RR/MDR-TB treatment

Management of ADRs associated with RR/MDR-TB is seen as an important component to achieve adherence resulting in favorable outcomes. ADRs should be picked up early by laboratory investigations to prevent future complications. Monitoring should be done regularly and intensively in high-risk patients such as HIV co-infected, diabetic, hypertensive, alcoholic, malnourished, kidney disease, liver disease, drug addicted and elderly patients. While most ADRs are minor and can be managed properly on an outpatient basis without cessation of medications, others may be major, severe or life threatening resulting in adjustment or cessation of medications or even mortality if not picked up and managed in time.[37]

1.2.3.5 Concordance between patient self-report and clinician record

Few studies have looked at the concordance between patient reports and clinicians' records/ medical record documentations.[46] Concordance between these sources of data have shown varied results and these agreements have been suggested to vary depending on characteristics of patients, source of information and type/ kind of information collected.[47] Concordance between patients reports and clinicians' reports/ medical documentation was seen to be higher in symptoms that could be observed directly like vomiting and diarrhoea than for subjective symptoms like fatigue and dyspnoea.[48] Clinicians reports are expected to be correct about treatments and other treatment issues associated with the disease of interest, but clinicians may not always be conscious of, or may under report or even over report the other health issues such as ADRs. [47] Previous reports show a discordance between patient self-report and the clinician report of ADRs to RR/MDR-TB treatment with the underreporting of patient ADRs documented in medical reports.[46] Other studies, outside the RR/MDR-TB settings like

in cancer, cardiac and kidney researches have also shown a discordance between patients self-report and clinician medical record documentation.[47,49]

1.2.3.6 Association between ADRs and RR/MDR-TB on treatment outcomes

ADRs can lead to clinician or patient interrupting, discontinuing or reducing the dosage of treatment before completion which may increase the risk lost to follow up, treatment failure or even death.[6] According to the WHO, treatment outcomes are defined as favorable or unfavorable.

Favorable treatment outcomes are:

Completed treatment: A RR/MDR-TB case having completed treatment with no indication of failure, no record showing sputum smear or culture results in the previous month of treatment was negative on at least one previous test whether due to test not carried out or results not seen. It can also be defined as recommended by the national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[50]

Cured: A bacteriologically confirmed RR/MDR-TB case at the initiation of treatment became smear or culture negative in the last month of treatment and at least one past occasion.[50]

Treatment success: The sum of cured and treatment completed.[50]

Unfavorable treatment outcomes are:

Loss to follow up (LTFU): A RR/MDR-TB case who did not begin treatment or stopped treatment for 2 consecutive months or more.[50]

Treatment failure: A RR/MDR-TB case who is smear or culture positive at 5 months or later during treatment. It can also be defined as treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of lack of conservation by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs).[50]

Death: A RR/MDR-TB case who died before initiating or within the treatment for any reason.[50]

Not evaluated: A patient for whom no treatment outcome is assigned, this includes cases "transferred out" to another treatment and whose treatment outcome is unknown.[50]

Treatment interruption can defined as any time a prescribed dose of MDR-TB medication is missed for at least a day but for less than 2 consecutive months.[51] Treatment interruption can be for short or long periods; short periods is referred to as intermittent interruption and long periods is referred to as lost to follow up. Both types of treatment interruption are major challenges in RR/MDR-TB treatment as they can result in high risk of severe illness, continued disease transmission, progression to extensive and total drug resistance (XDR and TDR) patterns, poor treatment outcomes and death.[52] Missed clinic appointments have been a major concern in the management of RR/MDR-TB since the roll-out of the outpatient decentralized RR/MDR-TB treatment which began late 2011 in South Africa. This could be due to accompanying morbidity, mortality or ADRs resulting in clinicians not being able to intervene as patients are not in clinic. Missed appointments can lead to treatment interruptions/ failure which could further amplify resistance, boost ongoing transmission and increase risk of morbidity and mortality.[53] Missed clinic appointments can add to the burden of the health care providers who already have difficulty in planning the patient load at clinics.[54]

1.3 Problem Statement

Global statistics show that the rates of treatment success for RR/MDR-TB are still very low, as low as 50% in different settings.[2] With an estimated increase of 480,000 new cases of RR/MDR-TB yearly, treatment failure and loss to follow-up results in public health problems.[2] Tolerating the treatment regimen is a big part of this problem as some patients describe the ADRs from RR/MDR-TB treatment as "*worse than the treatment itself*".[56,55] ADRs are considered to be one of the most significant problems with the treatment of RR/MDR-TB,[34,35] especially for sub-Saharan Africa, which has a high burden of HIV infection and the concomitant use of ART, increasing the risk of overlapping toxicities.[56] ADRs can result in the treatment interruption by patient or clinician, dosage reduction, and stopping of treatment before completion. This increases the risk of treatment failure, progression to XDR-TB, morbidity, and death.[4] The rate of ADRs associated with DR-TB treatment can be underestimated if there is discordance between the patient report and clinician record of ADRs. This can lead to poor patient management and lack of confidence in the RR/MDR-TB programs, resulting in poor TB treatment outcomes. For the RR/MDR-TB program, this could result in worse program indicators such as an increase in

transmission of RR/MDR-TB, attrition from RR/MDR-TB treatment, increase incidence of TB and HIV, and increase TB related deaths.[57]

In South Africa, there is a lack of data on the discordance between patient self-report and clinician record of ADRs to RR/MDR-TB and it is not clear if there is a relationship between a missed clinician record of ADRs to DR-TB treatment and poorer TB treatment outcomes such as poorer rates of retention, adherence, completion of treatment and subsequent cure.[46]

In light of the recent guideline changes, it is important to document the ADRs associated with the standard long-course regimen, the standard short-course regimen or the individualized (i.e., bedaquiline replaced kanamycin) long or short-course regimen accurately. This information is important as the countries decide whether to adopt oral or injectable regimen for RR/MDR-TB treatment into their national programs.[28]

1.4 Justification

Previous studies have reported discordances between patient self-report and clinician record of ADRs.[46] A more recent study from Kwa-Zulu Natal Province, South Africa, reported similar discordance results when comparing patient self-report and clinician record of ADRs during RR/MDR-TB treatment.[46] It is valuable to repeat the study in a different geographic location (such as Gauteng Province), especially where data is available on ADRs related to the newer RR/MDR-TB regimens. Gaps in knowledge still exist globally and in South Africa; therefore, this study will contribute to the existing body of knowledge on the discordance between patient self-report and clinician record of ADRs during RR/MDR-TB treatment. This information may also improve patient management during treatment as pharmacovigilance programs rely on the clinician's documentation of ADRs for RR/MDR-TB programs and policy formation.

1.5 Research Question

What is the degree of discordance between patient self-report and clinician report of ADRs? What is the relationship between missed clinician report of ADRs during DR-TB treatment and missed clinic appointments at an outpatient clinic in Johannesburg, South Africa?

1.6 Aims

To quantify discordance between patient self-report and clinician record of ADRs during DR-TB treatment and describe the relationship between missed clinician reports of ADRs to DR-TB treatment and missed clinic appointments at the TB Focal Point, an outpatient clinic at Helen Joseph Hospital in Johannesburg, South Africa, over a three-year period (02/2015 to 01/2018).

1.7 Objectives

1. To describe patient self-report and clinician record of ADRs during DR-TB treatment.

a. Describe ADRs disaggregated by patient characteristics (e.g., age, gender, HIV status, resistance patterns, DR-TB regimen, duration on treatment etc.)

2. To quantify the degree of the discordance between patient self-report and clinician record of ADRs during DR-TB treatment.
3. To describe the relationship between a missed clinician record of an ADRs and the likelihood of short-term outcome (missed clinic appointment) and long-term outcome (LTFU) in the following three months.

CHAPTER 2

2.0 Methodology

In this chapter, the study design, study population, setting and selection of the patient population, measurements and data sources are described. The key definitions, data management, statistical analysis and ethical considerations are also discussed.

2.1 Study design

This was a cross-sectional study comprised of two components. The first was a secondary analysis of data that was collected to describe the quality of life and self-reported adverse events among patients on RR-/MDR-TB treatment at Helen Joseph Hospital, Johannesburg, South Africa. The second, a medical record review to collect data on ADRs reported for the patients included in the aforementioned study sample.

2.2 Study setting and population

Study site: The outpatient TB clinic at Helen Joseph Hospital (HJH) was used for the purpose of this study. HJH is a public hospital situated in Auckland Park, Johannesburg, South Africa and it is affiliated to the University of the Witwatersrand's medical school. The hospital is responsible for the teaching of healthcare workers and providing tertiary health services in the Johannesburg community. The TB Focal Point at Helen Joseph Hospital is one of the three decentralized treatment centers for DR-TB in Gauteng province and provides integrated TB and HIV care.[58]

Study population: The study population were patients who were part of an ongoing prospective observational cohort at the TB outpatient clinic at the hospital between 2015 – 2018. These patients were also part of the Health Related Quality Of Life (HRQOL), a sub-study of the prospective cohort between February 2015 and January 2018 which was a coss-sectional study that enrolled patients on treatment when they returned to the clinic for routine clinic visit during the study period.

Sampling: No sampling strategy was used. The prospective cohort study started enrolling patients in March 2013. The cohort includes all adult (≥18 years) patients who initiated RR/MDR-TB treatment after March 2013, and patients are followed longitudinally until the earliest of death, lost to follow-up, treatment failure, or treatment completion. Patients who

were part of the two studies (i.e 149 DR-TB patients) were eligible to be included in the medical review, provided their patient files could be located at the TB focal point.

Figure 1: Aerial view of Helen Joseph Hospital in Johannesburg, South Africa.

An ongoing prospective cohort of DR-TB patients: The main cohort is an ongoing prospective observational cohort of DR-TB patients attending an outpatient clinic at Helen Joseph Hospital in Johannesburg, South Africa. The TB Focal Point at Helen Joseph Hospital is one of the three decentralized treatment centers for DR-TB in Gauteng province and provides integrated TB and HIV care.[58] The prospective cohort study started enrolling patients in March 2013. The cohort includes all adult (≥18 years) patients who initiated RR/MDR-TB treatment after March 2013, and patients are followed longitudinally until the earliest of death, lost to follow-up, treatment failure, or treatment completion.

Long course regimen: Implemented from 2011 – 2016. The treatment regimen for RR/MDR-TB includes the standard long-course which is 18 – 24 months long with daily injection of kanamycin for the first 6 months and 18 – 24 months of oral moxifloxacin, ethionamide, terizidone and pyrazinamide. The standard MDR-TB and RR-TB treatment is divided into two phases – intensive phase - 6 months using five drugs (kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide) followed by 12-18 months

(continuation phase) using four drugs (moxifloxacin, ethionamide, terizidone, and pyrazinamide). Provided the culture results are negative patients would then be initiated on the continuation phase (18 months) which consisted of: moxifloxacin, ethionamide, terizidone and pyrazinamide.[28,59]

Short course regimen: Implemented in 2016, following revision of the guideline, consists of a long and short regimen. Patients were initiated on the short regimen provided that they were diagnosed with RR-TB, never been on any second-line TB treatment for longer than one month and possess the inhA or katG mutation. The intensive phase (4 months) consisted of: kanamycin, moxifloxacin, clofazimine, ethionamide, high dose ethambutol, isoniazid, and pyrazinamide. The continuation phase (5 months) consisted of: clofazimine, pyrazinamide, moxifloxacin, and ethambutol. Patients previously exposed to second-line TB treatment were initiated on the longer regime for 18-20 months. The intensive phase (6-8 months) consisted of: moxifloxacin, kanamycin, pyrazinamide, terizidone and ethionamide. The continuation phase (≥ 12 months) was the same with the exclusion of kanamycin. The intensive phase for both regimens consisted of injectable drugs.[28,59]

All-oral regimen: In June 2018 South Africa, adopted the all-oral longer (18-20 months) and shorter (9-11 months) DR-TB regimens. The shorter regimen consists of an intensive phase (4-6 months) which includes the following: Bedaquilline (BDQ), levofloxacin both taken for the 6 months, linezolid (LZD) for only 2 months, clofazimine, high dose isoniazid (INHhigh dose), ethambutol and pyrazinamide and a continuation phase (5 months) consisting of levofloxacin (LFX), clofazimine (CFZ), ethambutol (E) and pyrazinamide (Z). Ethionamide is no more part of the short regimen. Bedaquiline substitutes the injectable drug for 6 months irrespective of the duration of the intensive phase and Levofloxacin substitutes Moxifloxacin also.[60] This shorter regimen is indicated in patients who have had prior exposure to second regimen is indicated in patients who have had prior exposure to second-line TB agents for 4 weeks or more and those with both inhA and katG mutations also.

The longer regimen similarly consists of an intensive phase (6-8 months) consisting of bedaquiline, levofloxacin, clofazimine, linezolid and terizidone, as well as a continuation phase (12 months) which if well tolerated includes levofloxacin, clofazimine and terizidone. LZD is given throughout the intensive and moxifloxacin is substituted for levofloxacin if

needed.[60] The longer regimen has the same indicators as that of the shorter regimen with the additional indication that the patient has resistance to the injectable agents.[28,59] In patients who have previously been on second-line drugs for more than a month, or who has been a contact of an MDR-TB patient with known resistance patterns, an individualized regimen should be used. These individualized regimen can be a short or long-course DR-TB regimen.[42]

Following RR/MDR-TB treatment initiation, a follow-up visit is scheduled at two weeks, with monthly follow-up conducted thereafter until treatment is completed. A month's supply of medication is given at each visit; daily injectable drugs are administered at the patient's primary health care clinic (PHC), which is typically a short distance from their home, during the intensive phase of therapy.

The aim of the cohort is to describe the cost and outcomes of RR-/MDR-TB treatment.[56] Cohort data is collected and recorded in an electronic TB patient record system, called the Focal Point Information System (FIS), which is maintained by the site. All participants provided written informed consent to participate in the cohort study and a unique study ID is assigned at enrollment in the cohort study. Information collected includes demographic characteristics, previous history of TB infection and treatment, HIV status and ART, TB molecular and culture-based testing, laboratory data, adverse events, chest x-rays, and audiometry testing results. Adverse events are documented in patient files by clinical providers as part of routine care.

Table Summarizing the evolution in treatment of RR/MDR-TB over time in South Africa.

Time periods	Regimens		
2011 - 2016	Standard long course	Intensive phase (6 months)	Continuation phase (12 - 18 months)
		Kanamycin, Moxifloxacin, Ethionamide, Terizidine Pyrazinamide	Moxifloxacin Ethionamide Terizidine Pyrazinamide
2016	Standard short course		
	Short regimen	Intensive phase (6 months)	Continuation phase (5months)
		Kanamycin	Clofazimide

		Moxifloxacin Clofazimine Ethionamide Ethambutol Isoniazid Pyrazinamide	Pyrazinamide Moxifloxacin Ethambutol
	Long regimen	Intensive phase (6 - 8 months	Continuation Phase (12 months)
		Moxifloxacin Kanamycin Pyrazinamide Terizidine Ethambutol	Moxifloxacin Pyrazinamide Terizidine Ethambutol
2018	All oral regimen		
	Short regimen	Intensive Phase (4 - 6 months)	Continuation Phase
		Bedaquilline Levofloxacin Linezolid Clofazimine Isoniazid Ethambutol Pyrazinamide	Levofloxacin Clofazimine Ethambutol Pyrazinamide
	Longer regimen	Intensive phase (6 – 8 months)	Continuation phase (12 months)
		Bedaquilline Levofloxacin Clofazimine Linezolid Terizidine	Levofloxacin Clofazimine Terizidine

Health-related quality of life (HRQOL) study: This was a sub-study of the prospective cohort described above conducted between February 2015 and January 2018. It was a cross-sectional study that enrolled patients on treatment when they returned to the clinic for a routine clinic visit during the study period. The eligibility criteria for this study were a laboratory confirmed diagnosis of rifampicin resistant TB, 18 years and older, registered for DR-TB treatment at Helen Joseph Hospital between February 2015 to January 2018 and had been enrolled in the prospective cohort study described above (i.e., had been assigned a

unique study ID). All participants provided written informed consent to participate in the sub-study.

Following patient informed consent, trained interviewers conducted face-to-face interviews using the Medical Outcomes Short Form-36 (SF-36) questionnaire for Health-Related Quality of Life (HRQOL) and the Patient-Reported Adverse Drug Event Questionnaire which is a verified tool to measure patient-reported ADRs.[31] The Patient-Reported Adverse Drug Event Questionnaire lists over 400 possible symptoms that a patient could experience in the past 4 weeks. For the analysis, the list of symptoms was reviewed by a clinician and symptoms were grouped into common ADRs associated with RR-/MDR-TB medication and those unrelated to RR-/MDR-TB medication. Patients were classified as having an ADR (any grade) if they reported any of the symptoms/ADRs that were identified as being associated with RR-/MDR-TB medication in the past 4 weeks. All data from patient interviews were collected on paper forms and later captured into REDCap, an electronic data capture tool, hosted by the University of the Witwatersrand, by study staff for data cleaning and analysis. Survey responses were linked to patient demographics using the unique study ID which was assigned at enrolment in the prospective observational cohort study and a single analytic dataset was created.

2.5 Data collection

Data for this study was obtained from three sources; (i) the ongoing prospective cohort electronic database, (ii) the HRQOL sub-study database and (iii) a database from the medical record review (Table 1.0). Data for this study comprised demographic/patient characteristics (i.e., disease classification, resistance pattern, treatment regimen etc.) and visit information obtained from the prospective cohort study dataset merged with data on patient self-report of ADRs obtained from the HRQOL sub-study dataset and clinician record of ADRs that was reported in patient files. The unique patient identifier was used to merge the three datasets into a single analytic dataset for analysis. Data on the clinician's record of ADRs were obtained from a retrospective medical record review of patients enrolled in the HRQOL sub-study (i.e., 149 DR-TB patients). An excel spreadsheet with a list of the unique study IDs and enrolment date into the HRQOL sub-study was obtained and used to extract the patient files from TBFP.

Once located, a data collection window was calculated, defined as any visit that occurred in the 4 weeks preceding the HRQOL sub-study enrolment and interview date – this time point was intended to capture ADRs recorded during the reporting period used in the HRQOL sub-study (i.e., symptoms or ADRs reported 4 weeks prior to the interview date). Any clinical notes reported during the data collection period were captured verbatim in an excel data collection tool, along with the visit date. Details of laboratory tests, laboratory results, investigations/procedures, concomitant medication prescribed or any other clinical notes recorded during the 4 weeks preceding the HRQOL sub-study visit were recorded in an Excel database.

The data collection procedures were finalized after a pilot study, whereby five patient files were extracted, the data collected, reviewed and the data collection tool revised. The researcher with a clinical background systematically collected and entered the data into the data collection tool. However, when needed, the clinical personnel on site were asked to help decipher and interpret the notes from the patient's files.[38] Thus the data for this study was from both secondary data and primary data. The secondary data was from the ongoing prospective cohort electronic database and the HRQOL sub-study database, while the primary data was collected by the primary researcher (student) with the help of other clinic staff. The ADRs was graded by the clinician as mild, moderate or severe in the patient's file and these were collected in the Excel database.

Medical record review of reported ADRs: Patients that were enrolled in the HRQOL sub-study between February 2015 and January 2018 (i.e., 149 DR-TB patients) were eligible to be included in the medical record review, provided that their patient files could be located at the tuberculosis focal point (TBFP). The patient file review was done between February and March 2020.

Laboratory results and concomitant medications recorded in the patient file were used to supplement the clinician report of ADR during the study period (4 weeks preceding the HRQOL sub-study visit). Where no clinician reports were available, laboratory results and concomitant medications (Table 2.0) were included with the results to define clinician report of ADRs. Appendix E shows the ADR that were extracted from the clinic notes in the patient file and the additional ADR that were identified from either laboratory results or concomitant medication using the classification outlined in Table 2.0. Since the main research question focused on patient self-report and clinician record of ADRs, the main analyses were restricted to only the clinician record of ADR.

Table 1.0: Table describing how data was collected from patient self-reports and clinician records.

Source	**Self-reports**	**Clinician record**
	Patients	**Medical records**
Data collection (how)	Patient interviews	File review
Data collection tool	REDCap	Excel
What data was collected	>400 symptoms	Verbatim from clinical notes
How was ADRs defined	ADRs were grouped into the following based on symptoms into visual disturbance, anemia, palpitations, nausea and vomiting, abdominal pain, diarrhea, rash, myalgia, joint pain, peripheral neuropathy, dizziness or vertigo, depression or mood disorder, psychosis, headache, insomnia, fatigue and hearing loss.	As documented in the medical, based on clinical notes, laboratory tests/results, concomitant medication or procedures/investigations and include hearing loss, psychosis, peripheral neuropathy, rashes, vomiting nausea, anemia, joint pain/arthralgia, palpitation/tachycardia, diarrhea, abdominal pain, myalgia, visual disturbance, vertigo, depression, headaches, insomnia, fatigue, ototoxicity, poor appetite, renal dysfunction, hypothyroidism, hyperthyroidism, gynecomastia, non-Hodgkin's lymphoma, skin toxicity, renal toxicity, weight gain, weight loss, liver toxicity, liver

		dysfunction, pancytopenia, gout, allergy, tinnitus and epilepsy

Data quality checks was carried out by me (the student) and cross checked by my supervisor at the beginning of data collection included: (i) making sure the study ID for the patient file extracted matched the unique study ID, and (ii) ensuring that clinician report and the visit date fell within the data collection window (i.e., four weeks prior to the patient interview). The researcher collecting the data did not have access to the HRQOL sub-study data (apart from the study IDs and interview date) until after the file review had been completed. Therefore, the primary researcher (student) did not have any prior knowledge of patient self-report of ADRs while collecting the clinical notes from the patient files.

2.6 Description of variables

2.6.1 Outcome variables

The main outcome variables (Objective 1 and 2) were patient self-report of ADRs and clinician record of ADRs during treatment for DR-TB. The variable ADR is defined as a dichotomous variable – if a patient or clinician reported any ADR then ADR was categorized as "Yes", whereas if no ADR was reported by the patient or the clinician then ADR was categorized as "No".

2.6.2 Exposure variables

Exposure variables were grouped as either patient demographic or clinical information. The patient demographic information was age, sex, employment status and educational status while the clinical information were resistance pattern, HIV status, duration on ART treatment, during on DR-TB treatment, baseline CD4 count, patient category, TB type, smear microscopy, diabetes, weight at treatment initiation, referring facility, and anemia.

Table : Showing the explanatory variables, categories and definition.

Variable	Categories	Definition
Age (Years)	18 – 35 >35	This was categorized based on the information given by the patient at the time of initiation of treatment.
Sex	Male Female	This was categorized based on the information given by the patient at the time of registration at initiation of

		treatment.
Employment status	Unemployed Employed Missing/Unknown	This was categorized based on the information given by the patient at the time of registration at initiation of treatment.
Educational level	Primary school or no education Secondary school or high school Higher than matriculation	This was categorized based on the information given by the patient at the time of registration at initiation of treatment.
Resistance pattern	MDR-TB (RIF and INH resistant) RIF resistant by Xpert MTB/RIF RIF mono-resistant (INH sensitive)	This was categorized according to the diagnostic methods used: rifampicin (RIF) resistant by Xpert MTB/RIF, MDR-TB (RIF and isoniazid resistant), or RIF mono-resistant (mono- or poly-resistance to RIF alone or RIF plus another first-line drug except isoniazid, confirmed by line probe assay or DST).
HIV status	HIV negative HIV positive HIV positive on ART HIV positive not on ART Unknown	This was categorized according to the HIV results recorded in the patient file. Unknown were those patients without HIV results recorded in the file.
Duration of ART treatment	≤ 6 months >6 months Missing	This was estimated from the time of start of treatment till the date of interview. Missing were those patients without the date of start of treatment recorded in file.
Duration of DR-TB treatment	≤ 6 months >6 months	This was estimated from the time of start of treatment till the date of interview.
DR-TB regimen	Standard long course Individualized long-course Standard short course Individualized short course	This was categorized as regimen taken as at the time of interview into standard or individualized (that is substituted for kanamycin) long or short course regimen.
Baseline CD4count	< 50 cells/mm^3 51 – 250 cells/mm^3 >250 cells/mm^3	This was categorized based on the most current result of CD4 test at the time of interview.
Patient category	New Previously treated Missing	This was categorized based on the information gotten at the time of interview whether patient was new to DR-TB treatment or have been on the treatment before. Missing were those patients without records of this.
TB type	PTB and EPTB or EPTB only PTB and not reported.	This was categorized based on the site of the TB infection: PTB (TB in the lungs) Extra pulmonary TB (EPTB) TB outside

		the lungs.
Smear microscopy	Negative Positive Unknown	This was categorized based on the result of sputum smear microscopy at the time of interview. Unknown were those patients without results recorded.
Diabetes	No Yes Missing/unknown	This was categorized based on the results of the blood sugar test recorded in the patients file at the time of initiation of treatment. Missing/unknown were those patients without any results.
Weight	< 50 kg >50kg Missing	This was categorized based on weight recorded in the patients file at the time of initiation of treatment.
Referring facility	Outpatient Inpatient	This was categorized based on the method of referral to the TB clinic. Outpatient were patients that were referred from outside hospital. Inpatient were patients that were referred from other departments of the hospital.
Anaemia	None or mild (Hb ≥11.0g/dl) Moderate (8 -10.9g/dl) or Severe (<8 g/dl) Missing	In defining anaemia, haemoglobin (Hb) was adjusted downward by 0.65 g/dl taking into consideration that Johannesburg is above sea level.[67]. This was categorized based according to WHO guidelines as none (Hb ≥12g/dl for non-pregnant women and Hb ≥13g/dl for men), moderate (8 -10.9g/dl) and severe (Hb <8g/dl).[44] Missing were those patients without any records on this.

2.7 Data management

An Excel data base was created to document the clinician report of ADRs. Firstly, five participants files were extracted, data collected and reviewed. The data collection tool was then revised with supervisors before continuing with the rest of the data collection. Data from the two studies, the main prospective cohort study (which contains the participants demographics and clinical characteristics) and the HRQOL sub-study (which contains participants self-reported ADRs) were merged and combined with the Excel data documenting the clinician report of ADRs to have a final analytic dataset using the study IDs. Missing data was dealt with at the analysis stage by restricting the analysis to participants who had a treatment outcome assigned (that is excluding those who were transferred out or missing outcome). For the self-report by participants (HRQOL sub-study data), all symptoms or complaints were reviewed by the clinicians and those not related to RR/MDR-TB

treatment were excluded. For the clinician's reports, clinicians were asked to help decipher and interpret the notes in the participant file.[38] If a participant file was not available or not found and if there were no records of ADRs in the patients file, the data was excluded and was not part of the final analytic dataset.

Confidentiality of the participants' information was preserved by removing identifiers (e.g., first name, surname, address, date of birth and gender). We validated the study IDs listed in the Excel spreadsheet documenting the clinician report of ADRs against the unique study IDs of the data from the HRQOL sub-study and the cohort study to confirm that they matched. To reduce bias, the researcher was blinded to the patient self-report of ADRs to DR-TB treatment until after the file review had been completed.

Table 2.0: Table showing laboratory data, medications and procedures/investigations suggesting ADRs to treatment.

	Classification	Potential ADRs
Laboratory data		
Hemoglobin	Mild 11-12.9 g/dl, moderate 8-10.9 g/dl and severe <8 g/dl	Anemia
Alanine transaminase (ALT) Aspartate transaminase (AST) Gamma glutamyl transferase GGT	ALT > 45 IU/L AST > 35 IU/L GGT > 30 IU/L	Liver toxicity
TSH, T4 or "free" T4 (FT4)	TSH ≥ 10 mU/L	Hypothyroidism
	TSH 0 – 0.4 mU/L	Hyperthyroidism
Serum creatinine Blood urea nitrogen (BUN)	Serum creatinine > 1.3 mg/dl BUN > 21mg/dl	Renal dysfunction/toxicity
Medication		
Vitamin B complex,		Peripheral neuropathy
Pyridoxine		Anemia
Loperamide		Diarrhea
Hydrochlorothiazide		Hypertension
Paracetamol/Ibuprofen		Pain
Dapsone		Rashes
Procedures/investigations		
Audiometry		Hearing loss/ototoxicity

ECG		Tachycardia

** g/dl – grams per deciliter, IU/L – International unit per liter, mU/L – milliunits per liter, mg/dl – milligrams per deciliter.

2.8 Data analysis

First, to describe participants included in the study, we used descriptive statistics to summarize demographic and clinical characteristics. Continuous variables were described using medians and interquartile ranges (IQR) where appropriate. Categorical variables were described using frequencies and percentages.

Second, to describe differences in demographic and clinical characteristics among those that had a record of ADRs and those that did not, we further disaggregated the patient characteristics by patient report of ADR (no ADR reported vs. ADR reported) and clinician record of ADR (no ADR reported vs. ADR reported) during RR/MDR-TB treatment.

Third, to describe the prevalence of ADRs, we calculated the percentages of the ADRs reported from patient self-report and clinician record of ADR to DR-TB treatment. This analysis was restricted to the signs and symptoms and diagnoses that were included in the patient interview for the HRQOL sub-study. The prevalence of ADRs was also graphically presented using histograms, stratified by source (patient self-report and clinician record) and DR-TB regimen (standard or individualized long course and standard or individualized short course).

Fourth, to determine the degree of concordance (agreement) between patient self-report and clinician record of ADR to DR-TB treatment, we used the Cohen's Kappa statistics (K), Gwet's agreement coefficient with first-order chance correction (AC1) and McNemar tests. Selection of ADRs to use for these tests was based on mutual reporting by the patients and clinicians. These tests were only performed when both patient self-report and clinician record had one or more ADRs documented (i.e., if either patient self-report or clinician record had zero ADRs documented, they were not included). These tests will be used to determine the degree of concordance (agreement) between the ADRs reported by patients and clinicians only.

Cohen's Kappa statistics is one of the commonest interrater reliability tests used to measure the degree of agreement between two raters. Kappa can range from -1 to +1. It can have values ≤ 0 showing no agreement, 0.0 - 0.20 as slight, 0.21 – 0.40 as fair, 0.41- 0.60 as moderate, 0.61 – 0.80 as considerable and 0.81 – 1.00 as nearly perfect agreement.[61]

Gwet's AC1 is a test for interrater reliability when there are many raters. It is similar to Kappa statistics but overcame the drawbacks of Kappa by providing a more robust measure of reliability. The interpretation of Gwet AC1 is similar to Kappa.[62] McNemar test is a non-parametric test for paired nominal data. It is used in finding a change in proportion for the paired data. It can be interpreted by reporting the p-value associated with the statistical inference and the relative risk with the 95% confidence interval.[63] These tests were used to determine the degree of agreement between the two reports.[46] With one rater being the patient and the other the clinician, an inter-rater reliability analysis was done.[46]

Lastly, to describe the relationship between a missed clinician records of ADRs and the likelihood of missing a clinic appointment in the following three months using multivariate logistic regression to estimate the odds ratio (OR) and corresponding 95% confidence intervals. Missed clinician record was identified by comparing the ADRs from patient self-report, and the ADRs from the clinician record and a dichotomous variable "missed clinician record of any ADR" was created. Where a patient reported any ADR but the clinician did not, "missed clinician record of any ADR" was coded at "1"; otherwise, "missed clinician record of any ADR" was coded as "0". Missed clinic appointment was defined as the patient missing (i.e., being ≥7 days late) for one or more of their follow-up clinics visits (within 3 months of their interview date). The crude and adjusted odds ratio (OR) and 95% confidence interval are presented.

$$\text{Magnitude of confounding} = \frac{RR_{crude} - RR_{adjusted}}{RR_{adjusted}}$$

Potential confounders (e.g., employment status, resistance pattern, DR-TB regimen, duration on DR-TB treatment, duration on ART treatment, diabetes, anemia, weight at the initiation of treatment, patient category, TB type and smear microscopy) with ≥10% magnitude of confounding along with *a priori* variables were considered in the multivariate analysis. *A priori* variables were those where a clinically meaningful relationship between the variable and the risk factor and between the variable and the outcome could be

established (regardless of statistical significance; e.g. sex,[64] age at initiation of treatment,[53] educational level,[53] HIV status,[53] and referring facility[53]).

All data analysis was done using Stata statistical software version 15 (Stata Corp, Texas, USA).

2.9 Ethical considerations

Ethical approval was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (Wits HREC M141188). Ethical approval was obtained from the provincial health authorities in charge of Helen Joseph Hospital and the National Department of Health, Johannesburg, South Africa. Patients provided written informed consent to participate in the cohort study and the HRQOL sub-study. This study was a retrospective review of programmatic data and a waiver of informed consent was granted to retrospectively review these records. Data were encrypted and protected using password on a computer that was only accessible to researcher and supervisors. Data is only used for academic purposes such as publication, conference presentations and policy briefs.

CHAPTER 3

Results

In this chapter, the results are presented according to the study objectives and the data analysis plan. It shows the descriptive statistics using tables and figures. The results are displayed chronologically based on the objectives of the study.

3.0 Baseline characteristics of study sample

We enrolled 149 participants for this study. The mean age of the participants was 37 years (standard deviation (SD) 10.2), 55.0% (n=82) were males, 42.3% (n=63) employed, and 75.8% (n=113) had secondary and high school education. Regarding HIV status, 77.9 % (n=116) were HIV positive, of which 81.0% (n=94) were on ART, and 71.3% (n=67) had been on ART for 6 months or more. Majority of the participants 61.8% (n=92) initiated treatment on the standard long-course while 22.1% (n=33) initiated treatment on an individualized long-course DR-TB treatment regimen. 45.0% (n=67) of the patients were RIF resistant (INH sensitive), 55.7% (n=83) had been on DR-TB treatment for more than 6

months, 60.4% (n=90) were new on treatment, 87.9% (n=131) had PTB only/PTB with EPTB, 66.4% (n=99) was negative on smear microscopy and 67.1% (n=100) was referred from the outpatient clinic (Table 3.0).

. For the primary analysis, we assumed that the absence of a clinician notes reporting an ADR in the patient file implied the absence of an ADR.

More female participants did not report ADRs while more male participants had clinicians' records of ADRs in their files. In total, males reported ADRs more 60.3% than the females 39.7%. Participants who were between 18 – 35 years and those greater than 35 years old reported ADRs equally 50% while those who were greater than 35 years had more records of ADRs from the clinicians 53.0%. More participants who were HIV positive 78.5% did not report ADRs themselves but had more clinicians record ADRs 78%. More participants with secondary school and higher level of education, 79% did not report ADRs but had more records of ADRs from clinicians 78%. Those who were unemployed reported ADRs more 38% and also had the highest number of ADRs recorded by the clinicians 59%.

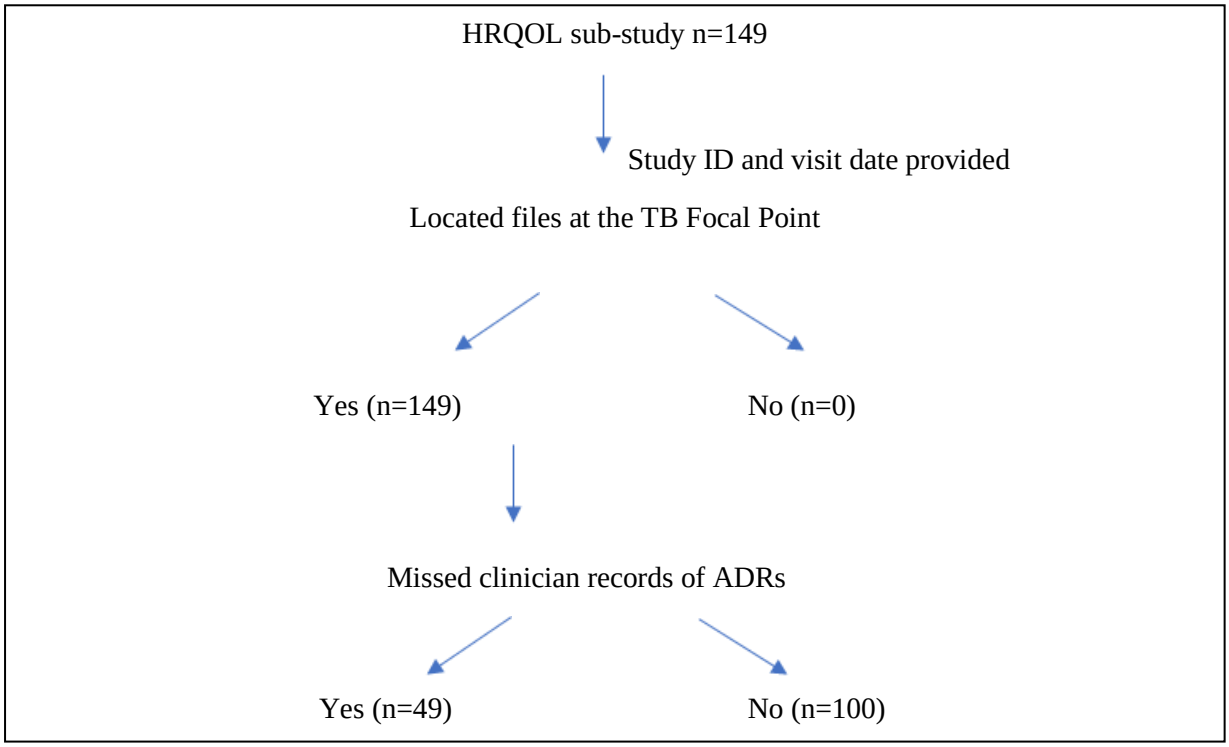

Figure 2 : Study sample showing missed clinician records of ADRs.

67% of participants on standard long-course did not report ADRs but had more clinicians' records of ADRs 56%. Of the participants that had been on DR-TB treatment for ≤6 months, they had less ADRs reported 37% but had more ADRs record from clinicians 51% compared with participants that were on ART treatment for >6 months who did not report ADRs but had more ADRs recorded by the clinicians. The newly diagnosed MDR-TB participants 57.1% did not report ADRs but had more clinicians' records of ADRs 62%. Participants without diabetes reported more ADRs 72.4% and also had more clinicians record of ADRs 71%. Those with weight above 50 kg reported more ADRs 65.5% and also had more clinician record of ADRs 69%. Patient with PTB (with or without EPTB) had more ADRs reported and clinicians record of ADRs 87.8% and 87% respectively (Table 3.0).

Baseline characteristics of patients who reported an AE versus those who did not (patient self-report; 58 versus 91) were largely similar, though patients who reported an AE were more likely to have moderate or severe anemia (from laboratory results) (<11 g/dL vs. ≥12 g/dL; RR 1.78 95% CI 1.03–3.08) and were less likely to have more than a secondary school education (RR 0.56 95% CI 0.36–0.89) (results previously published[6]).

Table 3.0a: Baseline characteristics of study sample

Patient's Characteristics	Total N = 149 n (%)
At DR-TB treatment initiation	
Sex	
Male	82 (55.0)
Female	67 (45.0)
Age at treatment initiation (years)	
18 -35	74 (49.7)
>35	75 (50.3)
Employment status	
Unemployed	85 (57.0)
Employed	63 (42.3)
Unknown	1 (0.7)
Educational level	
Primary school or no education	14 (9.4)
Secondary school and high school	113 (75.8)
Higher than matriculation	22 (14.7)
Resistance pattern	
MDR-TB (RIF and INH)	32 (21.5)
RIF resistant by Xpert MTB/RIF	38 (25.5)
RIF mono-resistant (INH sensitive)	67 (45.0)
Unknown	12 (8.1)
HIV status*	
HIV negative	27 (18.1)
HIV positive	116 (77.9)

HIV positive and on ART	94 (81.0)
HIV positive not on ART	22 (19.0)
Unknown	6 (4.0)
DR-TB regimen	
Standard long-course	92 (61.7)
Individualized long-course	33 (22.2)
Standard short-course	15 (10.1)
Individualized short-course	9 (6.0)
Diabetes	
No	109 (73.2)
Yes	6 (4.0)
Unknown	34 (22.8)
Anaemia	
None or mild	64 (43.0)
Moderate/severe	26 (17.5)
Unknown	59 (39.6)
Weight at treatment initiation (Kg)	
<50	37 (24.8)
≥50	103 (69.1)
Unknown	9 (6.0)
TB type	
PTB only/PTB with EPTB	131 (87.9)
EPTB	11 (7.3)
Unknown	7 (4.7)
Smear microscopy	
Negative	99 (66.4)
Positive	26 (17.5)
Unknown	24 (16.1)
Referring facility	
Outpatient	100 (67.1)
Inpatient	49 (32.9)
Patient category	
New	90 (60.4)
Previously treated	36 (24.2)
Unknown	23 (15.4)
At interview date	
Duration on DR-TB treatment (months)	
≤6	66 (44.3)
>6	83 (55.7)
Duration on ART treatment (months)	
≤6	14 (14.9)
>6	67 (71.3)
Unknown	13 (13.8)

*Among those who were HIV positive (n = 116); Hb haemoglobin, EPTB extra pulmonary TB, PTB pulmonary TB, ADR adverse drug reaction, RIF rifampicin, INH isoniazid

Table 3.0b: Patient reports of Adverse Drug Reaction (ADRs) to RR/MDR-TB treatment disaggregated by patients' characteristics.

Patient's	Total	Patients reports of ADRs	P values

Characteristics	N = 149 n (%)	n (%)		
		No ADRs reported (n = 91)	ADRs reported (n = 58)	
At DR-TB treatment initiation				
Sex				0.298
Male	82 (55.0)	47 (51.7)	35 (60.3)	
Female	67 (45.0)	44 (48.3)	23 (39.7)	
Age at treatment initiation (years)				0.948
18 -35	74 (49.7)	45 (49.5)	29 (50.0)	
>35	75 (50.3)	46 (50.5)	29 (50.0)	
Employment status				0.110
Unemployed	85 (57.0)	47 (51.6)	38 (65.5)	
Employed	63 (42.3)	43 (47.3)	20 (34.5)	
Missing / Unknown	1 (0.7)	1 (1.1)	0 (0.0)	
Educational level				0.041
Primary school or no education	14 (9.4)	5 (5.5)	9 (15.5)	
Secondary school and high school	113 (75.8)	72 (79.1)	41 (70.6)	
Higher than matriculation	22 (14.7)	14 (15.3)	8 (13.7)	
Resistance pattern				0.719
MDR-TB (RIF and INH)	32 (21.5)	22 (24.2)	10 (17.2)	
RIF resistant by Xpert MTB/RIF	38 (25.5)	22 (24.2)	16 (27.6)	
RIF mono-resistant (INH sensitive)	67 (45.0)	39 (42.9)	28 (48.3)	
Missing	12 (8.1)	8 (8.8)	4 (6.9)	
HIV status*				0.213
HIV negative	27 (18.1)	18 (19.8)	9 (15.5)	
HIV positive	116 (77.9)	69 (75.8)	47 (81.0)	
HIV positive and on ART	94 (81.0)	60 (87.0)	34 (72.3)	
HIV positive not on ART	22 (19.0)	9 (13.0)	13 (27.7)	
Unknown	6 (4.0)	4 (4.4)	2 (3.5)	
DR-TB regimen				0.337
Standard long-course	92 (61.7)	61 (67.0)	31 (53.5)	
Individualized long-course	33 (22.2)	17 (18.7)	16 (27.6)	
Standard short-course	15 (10.1)	9 (9.9)	6 (10.3)	
Individualized short-course	9 (6.0)	4 (4.4)	5 (8.6)	
Diabetes				0.799
No	109 (73.2)	67 (73.6)	42 (72.4)	
Yes	6 (4.0)	4 (4.4)	2 (3.5)	
Missing	34 (22.8)	20 (22.0)	14 (24.1)	
Anaemia				0.060
None or mild	64 (43.0)	46 (50.5)	18 (31.0)	
Moderate/severe	26 (17.5)	13 (14.3)	13 (22.4)	
Missing	59 (39.6)	32 (35.2)	27 (46.6)	

Weight at treatment initiation (Kg)				0.258
<50	37 (24.8)	19 (20.9)	18 (31.0)	
≥50	103 (69.1)	65 (71.4)	38 (65.5)	
Missing	9 (6.0)	7 (7.7)	2 (3.4)	
TB type				0.764
PTB only/PTB with EPTB	131 (87.9)	80 (87.9)	51 (87.9)	
EPTB	11 (7.3)	6 (6.5)	5 (8.6)	
Unknown	7 (4.7)	5 (5.4)	2 (3.4)	
Smear microscopy				0.433
Negative	99 (66.4)	57 (62.6)	42 (72.4)	
Positive	26 (17.5)	17 (18.7)	9 (15.5)	
Unknown	24 (16.1)	17 (18.7)	7 (12.1)	
Referring facility				0.740
Outpatient	100 (67.1)	62 (68.1)	38 (65.5)	
Inpatient	49 (32.9)	29 (31.9)	20 (34.5)	
Patient category				0.541
New	90 (60.4)	52 (57.1)	38 (65.5)	
Previously treated	36 (24.2)	23 (25.3)	13 (22.3)	
Missing	23(15.4)	16(17.6)	7 (12.1)	
At interview date				
Duration on DR-TB treatment (months)				0.263
≤6	66 (44.3)	37 (40.7)	29 (50.0)	
>6	83 (55.7)	54 (59.3)	29 (50.0)	
Duration on ART treatment (months)				0.719
≤6	14 (14.9)	9 (15.0)	5 (14.7)	
>6	67 (71.3)	44 (73.3)	23 (67.7)	
Missing	13 (13.8)	7 (11.7)	6 (17.7)	

Table 3.0c: Clinicians records of Adverse Drug Reactions (ADRs) to RR/MDR-TB disaggregated by patient characteristics.

Patient's Characteristics	Total N = 149 n (%)	Clinician records of ADRs n (%)		P values
		No ADRs recorded (n = 49)	ADRs recorded (n = 100)	
At DR-TB treatment initiation				
Sex				0.717
Male	82 (55.0)	28 (57.1)	54 (54.0)	
Female	67 (45.0)	21 (42.9)	46 (46.0)	
Age at treatment initiation (years)				0.353
18 -35	74 (49.7)	27 (55.1)	47 (47.0)	
>35	75 (50.3)	22 (44.9)	53 (53.0)	
Employment status				0.449
Unemployed	85 (57.0)	26 (53.1)	59 (59.0)	
Employed	63 (42.3)	23 (46.9)	40 (40.0)	
Unknown	1 (0.7)	0 (0.0)	1 (1.0)	
Educational level				0.152
Primary school or no education	14 (9.4)	7 (14.3)	7 (7.0)	
Secondary school and high school	113 (75.8)	35 (71.4)	78 (78.0)	
Higher than	22 (14.7)	7 (14.2)	15 (15.0)	

matriculation				
Resistance pattern				0.032
MDR-TB (RIF and INH)	32 (21.5)	8 (16.3)	24 (24.0)	
RIF resistant by Xpert MTB/RIF	38 (25.5)	7 (14.3)	31 (31.0)	
RIF mono-resistant (INH sensitive)	67 (45.0)	30 (61.2)	37 (37.0)	
Unknown	12 (8.1)	4 (8.2)	8 (8.0)	
HIV status*				1.000
HIV negative	27 (18.1)	9 (18.4)	18 (18.0)	
HIV positive	116 (77.9)	38 (79.2)	78 (78.0)	
HIV positive and on ART	94 (81.0)	31 (81.6)	63 (80.8)	
HIV positive not on ART	22 (19.0)	7 (18.4)	15 (19.2)	
Unknown	6 (4.0)	2 (4.1)	4 (4.0)	
DR-TB regimen				0.133
Standard long-course	92 (61.7)	36 (73.5)	56 (56.0)	
Individualized long-course	33 (22.2)	7 (14.3)	26 (26.0)	
Standard short-course	15 (10.1)	5 (10.2)	10 (10.0)	
Individualized short-course	9 (6.0)	1 (2.0)	8 (8.0)	
Diabetes				0.939
No	109 (73.2)	38 (77.6)	71 (71.0)	
Yes	6 (4.0)	2 (4.1)	4 (4.0)	
Unknown	34 (22.8)	9 (18.4)	25 (25.0)	
Anaemia				0.704
None or mild	64 (43.0)	23 (47.0)	41 (41.0)	
Moderate/severe	26 (17.5)	7 (14.3)	19 (19.0)	
Unknown	59 (39.6)	19 (38.8)	40 (40.0)	
Weight at treatment initiation (Kg)				0.998
<50	37 (24.8)	12 (24.5)	25 (25.0)	
≥50	103 (69.1)	34 (69.4)	69 (69.0)	
Unknown	9 (6.0)	3 (6.1)	6 (6.0)	
TB type				0.672
PTB only/PTB with EPTB	131 (87.9)	44 (89.8)	87 (87.0)	
EPTB	11 (7.3)	3 (6.1)	8 (8.0)	
Unknown	7 (4.7)	2 (4.0)	5 (5.0)	
Smear microscopy				0.668
Negative	99 (66.4)	34 (69.4)	65 (65.0)	
Positive	26 (17.5)	9 (18.4)	17 (17.0)	
Unknown	24 (16.1)	6 (12.2)	18 (18.0)	
Referring facility				0.679
Outpatient	100 (67.1)	34 (69.4)	66 (66.0)	
Inpatient	49 (32.9)	15 (30.6)	34 (34.0)	
Patient category				0.677
New	90 (60.4)	28 (57.1)	62 (62.0)	
Previously treated	36 (24.2)	14 (28.6)	22 (22.0)	
Unknown	23(15.4)	7 (14.3)	16 (16.0)	
At interview date				

Duration on DR-TB treatment (months)				0.019
≤6	66 (44.3)	15 (30.6)	51 (51.0)	
>6	83 (55.7)	34 (69.4)	49 (49.0)	
Duration on ART treatment (months)				0.059
≤6	14 (14.9)	7 (22.6)	7 (11.1)	
>6	67 (71.3)	23 (74.2)	44 (69.8)	
Unknown	13 (13.8)	1 (3.2)	12 (19.1)	

*Among those who were HIV positive (n = 116); Hb haemoglobin, EPTB extra pulmonary TB, PTB pulmonary TB, ADR adverse drug reaction, RIF rifampicin, INH isoniazid

3.1 Distribution of ADRs obtained from patient self-report and clinician record

Results from patient self-report of ADRs showed that 38.9% (58/149) reported a total of 122 ADRs. Using the total number of ADRs reported (n=122) as the denominator, joint pain 14.8% (n=22), peripheral neuropathy 10.7% (n=16), hearing loss 10.1% (n=15), nausea and vomiting 8.1% (n=12) and vertigo 7.4% (n=11) were the most common. The clinician record of ADRs showed that 67.1% (100/149) reported a total of 141 ADRs. Using the total number of ADRs reported (n=141) as the denominator, hearing loss 38.9% (n=58), peripheral neuropathy 4.0% (n=6), joint pain/arthralgia 3.4% (n=5), anemia 2.0 (n=3) and nausea 1.3% (n=2) were the most common (Table 3.1). Results suggest that clinician record of ADRs underestimated the actual incidence of ADRs in patients on DR-TB treatment (Appendix E). When using laboratory results and concomitant medications to supplement the clinical notes, the total number of ADRs from the clinician record increased by 103 ADRs. The most common ADRs that were identified from laboratory tests or medication but were not reported in the patient file are anemia (n=32), arthralgia/joint pain (=22), and renal dysfunction (n=12) (Appendix E).

Table 3.1: Distribution of ADRs obtained from patient self-report and clinician record.

Adverse drug reactions	Patient self-report (n/N, %)	Clinician record (n/N, %)
Hearing loss	15 (10.1)	58 (38.9)
Psychosis	2 (1.3)	2 (1.3)
Peripheral Neuropathy	16 (10.7)	6 (4.0)
Rashes	5 (3.4)	1 (0.7)
Vomiting	12 (8.1)	1 (0.7)

Nausea	12 (8.1)	2 (1.3)
Anemia	1 (0.7)	3 (2.0)
Joint pain /Arthralgia	22 (14.8)	5 (3.4)
Palpitation / Tachycardia	1 (0.7)	1 (0.7)
Diarrhea	2 (1.3)	0 (0)
Abdominal pain	2 (1.3)	0 (0)
Myalgia	10 (6.7)	0 (0)
Visual disturbance	4 (2.7)	0 (0)
Vertigo	11 (7.4)	0 (0)
Depression	9 (6.0)	0 (0)
Headaches	2 (1.3)	0 (0)
Insomnia	2 (1.3)	0 (0)
Fatigue	6 (4.0)	0 (0)
Poor appetite	0 (0)	1 (0.7)
Weight gain	0 (0)	1 (0.7)
Weight loss	0 (0)	1 (0.7)
Allergy	0 (0)	1 (0.7)
Tinnitus	0 (0)	2 (1.3)

The above table was restricted to the ADRs that were elicited from the patient self-report (i.e., asked about during the patient interviews). Some additional ADRs were extracted from clinician's records and these included renal dysfunction, hypothyroidism, hyperthyroidism, gynecomastia, non-Hodgkins lymphoma, skin toxicity, renal toxicity, liver toxicity, liver dysfunction, pancytopenia, gout, allergy and epilepsy.

Of all the ADRs reported, only 9 ADRs were reported by both patients and clinicians, hearing loss was mostly reported by the clinician while joint pain was mostly reported by patients. Psychosis and palpitations/tachycardia was reported equally by both patients and clinicians (Figure 3).

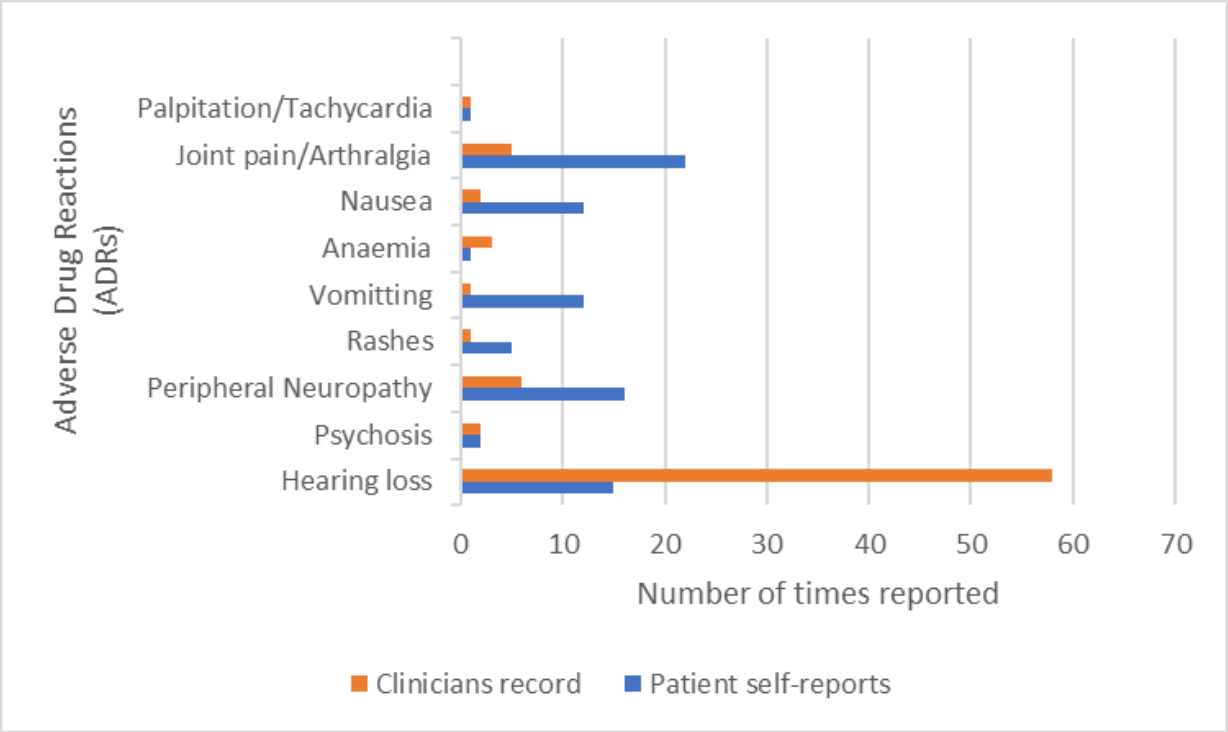

Figure 3: Prevalence of ADRs obtained from patient self-reports and clinician record.

While only 16% (24/149) of the participants were on a short DR-TB regimen (standard or individualized), joint pain/arthralgia, nausea, anaemia, vomiting and peripheral neuropathy were the main adverse events reported by these participants. .

Figure 4 compares the ADRs reported by patients on either a long regimen or short regimen (standard or individualized) for DR-TB.

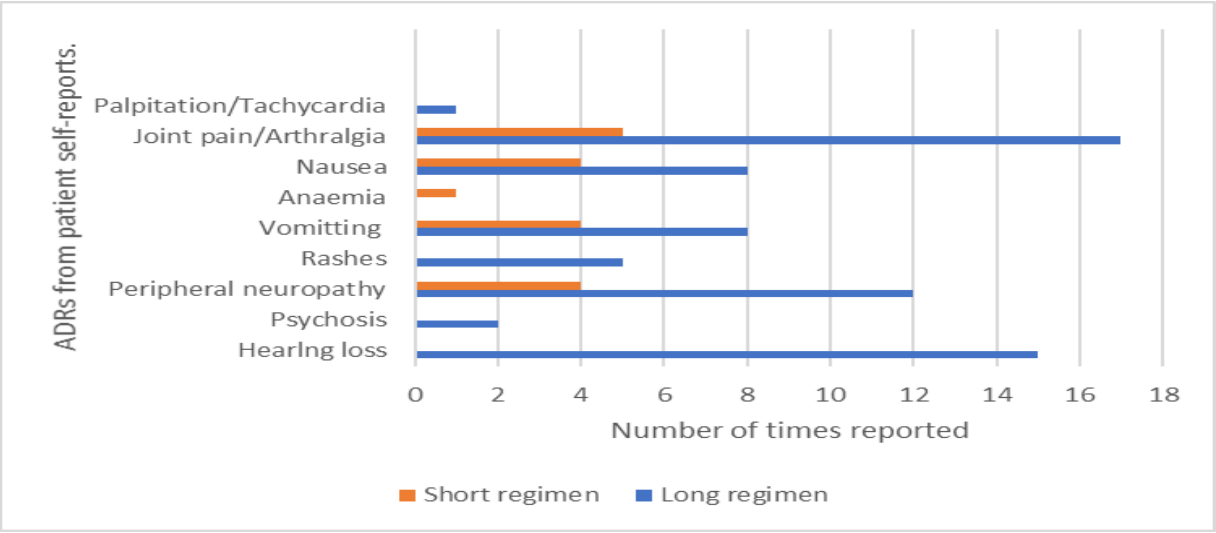

Figure 4 : Prevalence of ADRs from patient self-report by DR-TB regimen.

For patients on a long regimen for DR-TB, ADRs from the clinician record included joint pain/arthralgia, anaemia, vomiting, rashes, peripheral neuropathy, psychosis and hearing loss. For those on a short regimen for DR-TB, palpitation/tachycardia and nausea, (which were not reported for patients on a long regimen), pain/arthralgia, peripheral neuropathy and hearing loss were reported. For Figure 5 below, patients had a mix of short regimen with injectable (linked to hearing loss) for a while (2016) and then switched over to the all oral (injection free) regimen later in 2018. Hearing loss can be present in individuals with DR-TB even before the initiation of anti-TB treatment. But exposure to ototoxic drugs, like kanamycin, damages the structures of the inner ear and causes hearing loss.

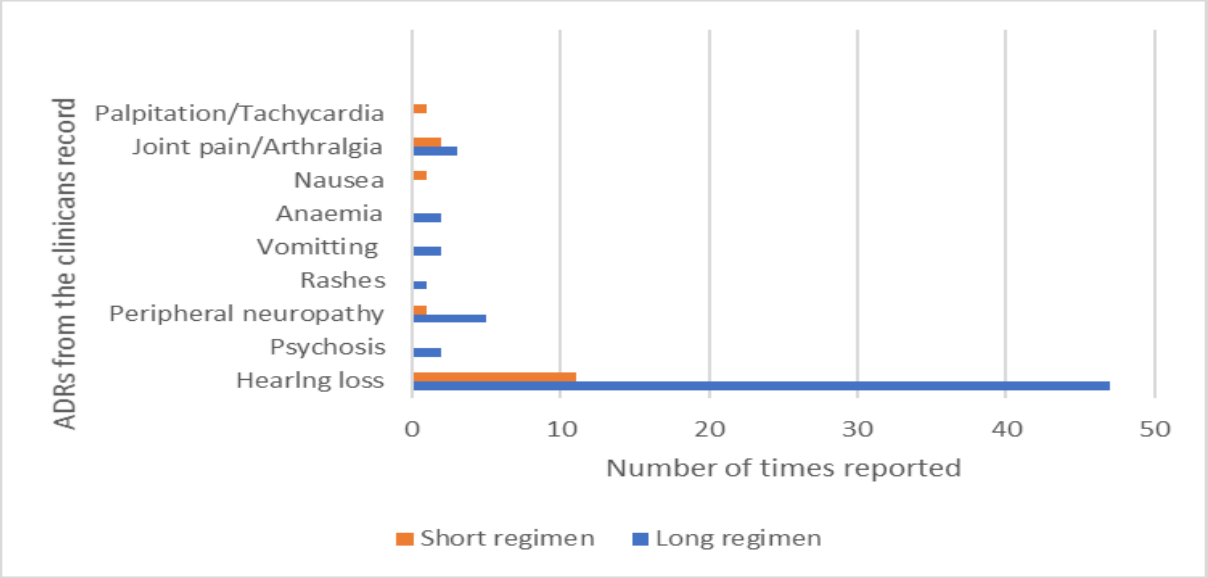

Figure 5: Prevalence of ADRs from clinician record by DR-TB regimen.

3.2 Concordance of ADRs between patient self-report and clinician record of ADRs during DR-TB treatment

The concordance between the patient self-report and clinician record of ADRs are presented in Table 3 and only those ADRs that were reported by both patient and the clinician are included. Kappa scores ranged from -0.01 (poor) to 0.49 (moderate), AC1 scores ranged from 0.39 to 0.99, percentage agreement ranged from 62% to 99%. Other ADRs were found to be statistically significant except for psychosis (p=0.99), anaemia (p=0.31) and palpitation/tachycardia (p=0.99).

ADRs with the greatest concordance between patient self-report and clinician record based on kappa was psychosis (kappa=0.49) and rashes (kappa=0.33) and peripheral neuropathy

(kappa=0.13). Psychosis and palpitation/tachycardia had the highest overall agreement of 99% from both sources although palpitation/tachycardia had a low kappa of -0.01. The ADRs with the highest Gwet's AC1 scores of 0.99 were psychosis and peripheral neuropathy while hearing loss had the lowest score of 0.39 (Table 3.2).

Table 3.2: Concordance between patient self-report and clinician record of ADRs.

ADRs	Patient self-report N (%)	Clinician record N (%)	Kappa (95% CI)	Kappa categories	Gwet's AC1 (95% CI)	McNemar's Test (p-value)
Signs and symptoms						
Rashes	5 (3.4)	1 (0.7)	0.33 (-0.16 - 0.81)	Fair	0.97 (0.94 - 1.00)	0.0455
Vomiting	12 (8.1)	1 (0.7)	-0.01 (-0.04 - 0.01)	None	0.90 (0.85 - 0.96)	0.0023
Nausea	12 (8.1)	2 (1.3)	-0.02 (-0.05 - 0.01)	None	0.90 (0.84 - 0.95)	0.0075
Joint pain/ Arthralgia	22 (14.8)	5 (3.4)	0.26 (0.04 - 0.47)	Fair	0.85 (0.77 - 0.92)	0.0001
Palpitation/ Tachycardia	1 (0.7)	1 (0.7)	-0.01 (-0.02 - 0.00)	None	0.99 (0.99 - 1.00)	1.0000
Diagnosis						
Hearing loss	15 (10.1)	58 (38.9)	0.07 (-0.05 - 0.19)	Slight	0.39 (0.23 - 0.55)	<0.0001
Psychosis	2 (1.3)	2 (1.3)	0.49 (-0.11 - 1.00)	Moderate	0.99 (0.97 - 1.00)	1.0000
Peripheral Neuropathy	16 (10.7)	6 (4.0)	0.13 (-0.09 - 0.35)	Slight	0.86 (0.79 - 0.92)	0.0184
Anaemia	1 (0.7)	3 (2.0)	-0.01 (-0.03 - 0.01)	None	0.97 (0.94 - 1.00)	0.3173

** Values of Kappa scores ≤ 0 showing no agreement, 0.0 - 0.20 as slight, 0.21 – 0.40 as fair, 0.41- 0.60 as moderate, 0.61 – 0.80 as considerable and 0.81 – 1.00 as nearly perfect agreement.

3.3 Association between missed clinician record of ADRs and missed clinic appointment

The association between missed clinician record of ADRs and missed clinic appointment are presented in Table 3.3.

We noted that 83 (44%) did not miss any clinic visit date, 20 (13.4%) had missed one clinic visit while 37 (24.8%) had missed two clinic visits reported in the patient file in the 4 weeks prior to the interview date. We compared characteristics of those that had a clinic visit (n=83) to those that did not (n=66) using the chi-square test of independence (Appendix H). Characteristics such as age at treatment initiation, employment status, education, resistance pattern, HIV status, DR-TB regimen, weight at treatment initiation, referring facility and patient category were largely similar, although patients that had a clinic visit were more

likely to have a missing/unknown smear status at the start of TB treatment (26.0% versus 8.4%; OR 1.80 95% CI 1.29 – 2.53).

Compared to patients where the clinician recorded the ADR in the patient file, a lower proportion of patients where the clinician did not record the ADR in the patient file went on to miss their subsequent clinic appointment (within 3 months) (65.1% versus 51.9% OR 0.57 95% CI 0.27 – 1.20; p = 0.14). After adjusting for sex, age at initiation of treatment, education level, resistance pattern, duration on ART treatment, referring facility and HIV status, our results showed that compared to not missing a record of an ADR, missing a record of an ADR in the patient file was not associated with missing a subsequent visit (aOR 0.43, 95% CI 0.13 – 1.34 p = 0.148).

From the univariate analysis, our results also showed that compared to patients who were RIF resistant by Xpert MTB/RIF, those who were RIF mono-resistant (INH sensitive) were less likely to miss their subsequent visit (OR 0.25, 95% CI 0.09 – 0.66; p=0.005). Compared to those on DR-TB treatment for less than 6 months, those on treatment for 6 or more months were less likely to miss their subsequent visit (OR 0.43, 95% CI 0.21 – 0.90; p=0.027). After adjusting, only patients who were RIF mono-resistant (INH sensitive) were less likely to miss their subsequent visit (aOR 0.21 95% 0.05 – 0.82; p=0.026).

Table 3.3: Association between missed clinician record of ADRs and missed clinic appointments (n=83).

Variables	Proportion with the outcome N = 83, n (%)	Proportion without the outcome N = 66, n (%)	Crude Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)
Missed clinicians' records of ADRs					
Not missed (ref)	28 (65.12)	15 (34.88)	1.00		1.00
Missed	55 (51.89)	51 (48.11)	0.71 (0.35 – 1.43)	0.343	0.43 (0.13 – 1.34
Sex					
Males (ref)	46 (56.10)	36 (43.90)	1.00		1.00
Females	37 (55.22)	30 (44.78)	1.13 (0.56 – 2.26)	0.723	1.05 (0.33 – 3.2)
Age at initiation of treatment					
18 – 35 (ref)	37 (50.00)	37 (50.00)	1.00		1.00
>35	46 (61.33)	29 (38.67)	1.44 (0.33 – 1.38)	0.288	0.74 (0.23 – 2.32
Employment status					
Unemployed (ref)	50 (58.82)	35 (41.18)	1.00		
Employed	33 (50.79)	31 (49.21)	0.74 (0.37 – 1.48)	0.400	
Education level					
Primary school or no	9 (64.29)	5 (35.71)	1.00		

education (ref)					
Secondary school and high school	63 (55.75)	50 (44.25)	2.17 (0.70 – 6.71)	0.175	
Higher than matriculation	11 (50.00)	11 (50.00)	2.05 (0.51 – 8.22)	0.307	
Resistance pattern					
RIF resistant by Xpert MTB/RIF (ref)	26 (68.42)	12 (31.58)	1.00		
RIF mono-resistant (INH sensitive)	35 (52.24)	32 (47.76)	0.25 (0.09 – 0.66)	0.005	0.21 (0.05 – 0.82
MDR-TB (RIF and INH)	18 (56.25)	14 (43.75)	0.63 (0.20 – 2.01)	0.442	0.79 (0.16 – 3.71
Missed	4 (33.33)	8 (66.67)	0.37 (0.08 – 1.66)	0.196	
HIV status					
HIV negative (ref)	13 (48.15)	14 (51.85)	1.00		
HIV positive and on ART	57 (60.64)	37 (39.36)	1.06 (0.42 – 2.64)	0.900	
HIV positive and not on ART	10 (45.45)	12 (54.55)	1.06 (0.31 – 3.54)	0.922	
Unknown	3 (50.0)	3 (50.0)	1.00 (0.15 – 6.61)	0.995	
DR-TB regimen					
Standard long-course (ref)	57 (61.96)	35 (38.04)	1.00		
Individualized long-course	15 (45.45)	18 (54.55)	2.31 (0.89 – 5.90)	0.082	2.26 (0.51 – 9.98
Standard short-course	7 (46.67)	8 (53.33)	1.22 (0.38 – 3.95)	0.714	2.83 (0.23 – 28.2
Individualized short-course	4 (44.44)	5 (55.56)	4.93 (0.59 – 41.49)	0.140	2.38 (0.10 – 51.7
Duration on DR-TB treatment (months)					
<6 (ref)	31 (46.97)	35 (53.03)	1.00		1.00
>6	52 (62.65)	31 (37.35)	0.43 (0.21 – 0.90)	0.027	0.32 (0.08 – 1.31
Duration on ART treatment (months)					
< 6 (ref)	9 (64.29)	5 (35.71)	1.00		1.00
>6	42 (62.69)	25 (37.31)	1.93 (0.59 – 6.32)	0.276	3.39 (0.31 – 6.17
Unknown	6 (46.15)	7 (53.85)	11.06 (1.09 – 111.84)	0.042	0.94 (0.29 – 3.03
Diabetes					
No (ref)	64 (58.72)	45 (41.28)	1.00		
Yes	5 (83.33)	1 (16.67)	1.11 (0.19 – 6.43)	0.903	
Anaemia					
None or mild (Hb > 11.0g/dl) (ref)	36 (56.25)	28 (43.75)	1.00		1.00
Moderate (8 - 10.9g/dl)	10 (38.46)	16 (61.54)	1.44 (0.52 – 3.98)	0.480	1.39 (0.31 – 6.17
Missing	37 (62.71)	22 (37.29)	1.20 (0.56 – 2.55)	0.625	0.94 (0.29 – 3.03
Weight at treatment initiation (Kg)					
<50 (ref)	61 (59.22)	42 (40.78)	1.00		
>50	18 (48.65)	19 (51.35)	0.99 (0.44 – 2.22)	0.982	
Unknown	4 (44.44)	5 (55.56)	0.93 (0.21 – 4.01)	0.930	
TB type					
PTB only/PTB with EPTB	4 (57.14)	3 (42.86)	0.78 (0.14 – 4.25)	0.782	
EPTB	74 (56.49)	57 (43.51)	1.02 (0.12 – 8.52)	0.981	
Unknown (ref)	5 (45.45)	6 (54.55)	1.00		

Smear microscopy					
Negative (ref)	61 (61.62)	38 (38.38)	1.00		
Positive	15 (57.69)	11 (42.31)	0.97 (0.39 – 2.42)	0.961	
Unknown	7 (29.17)	17 (70.83)	1.43 (0.50 – 4.05)	0.496	
Referring facility					
Outpatient (ref)	59 (59.00)	41 (41.00)	1.00		
Inpatient	24 (48.98)	25 (51.02)	1.13 (0.53 – 2.37)	0.744	
Patient category					
New (ref)	48 (53.33)	42 (46.67)	1.00		1.00
Previously treated	24 (66.67)	12 (33.33)	0.73 (0.32 – 1.66)	0.462	0.61 (0.18 – 2.01
Unknown	11 (47.83)	12 (52.17)	1.01 (0.37 – 2.75)	0.976	1.24 (0.07 – 20.3

Abbreviations: ART – Antiretroviral therapy, DR-TB - Drug Resistant Tuberculosis, EPTB – Extra Pulmonary Tuberculosis, HIV - Human immunodeficiency Virus, INH – Isoniazid, MDR-TB – Multidrug Resistant Tuberculosis, MTB – Mycobacterium Tuberculosis, OR – Odds Ratio, PTB – Pulmonary Tuberculosis, ref – Reference, RIF – Rifampicin, TB – Tuberculosis.

We then restricted the analysis to only those patients that had a clinic visit file in the 4 weeks preceding the interview date (Figure 1; Table 3.4). From this univariate analysis, the estimate (OR 0.72, 95% CI 0.23 – 2.19; p = 0.557) was similar to that obtained for the complete analysis (n=149; OR 0.71, 95% CI 0.35 – 1.43; p = 0.343), but the confidence interval was much wider indicating greater uncertainty or a less precise estimate.

Table 3.4: Association between missed clinician record of ADRs and missed clinic appointment, among patient that missed a clinic visit (n=100).

Clinician record of ADRs	**Missed clinic appointments**		**Crude Odds Ratio**
	No N (%)	Yes N (%)	
Not missed	6 (40.0%)	9 (60.0%)	1.00
Missed	41 (48.2%)	44 (51.8%)	0.72 (0.23 – 2.19); p=0.557

CHAPTER 4

Discussion

The focus of chapter one was to briefly introduce TB and RR/MDR-TB, their burdens, classifications, diagnosis, and treatment. The methods and results of this study are in chapter two and three respectively. The purpose of this chapter is to discuss the findings of the study and describe how they relate to existing knowledge and previous studies. It will also elaborate on the contributions that this study makes to the public health field.

4.0 Prevalence of ADRs

The findings from this study are in contrast with prior findings from patient populations outside the TB settings and this study is believed to be one of few studies in South Africa looking at the concordance between patient self-report and clinician record of ADRs to RR/MDR-TB treatment.

Overall, in this study the prevalence of ADRs from clinician record (medical records) was seen to be higher than that of patient self-report (interviews) and this is in contrast with some studies[32,46]. This study reported ADRs prevalence of 39% from patient self-report and 67% from clinical record which are not similar to previous study which reported a prevalence of ADRs to be 99% from patient interviews and 81% from medical reports.[32] A more recent study done in South Africa also reported the prevalence of ADRs to be 98% from patient interviews and 78% from medical reports.[11,46] This may have been from the fact that clinician record of ADRs (medical records) was objective from laboratory investigations like audiometry unlike patient self-report (interviews) which was subjective just from patients experience and recalls.

In comparing the methods used for data collection in other studies to the one used in our study, some are similar even though these studies were not in DR-TB populations.[11,32,46]

Table 4.0: Comparing the ADRs reported in this study to other studies.

ADRs	This report (%)	Paper 1 (%) [32]	Paper 2 (%) [46]	Paper 3 (%) [11]
Arthralgia	9.8	67.5	72	-
Hypothyroidism	9.9	19.7	-	-
Ototoxicity	6.2	5.9	26	17.3
Peripheral Neuropathy	8.0	1.1	18	6.1
Psychiatric disorders	1.5	0.4	-	6.7

Nephrotoxicity	2.9	1.9	-	10.3
Insomnia	1.3	-	67	-
Visual impairment	2.7	2.5	62	-
Hearing loss	26.5	-	-	53.5

Hearing loss was reported as the most common ADRs with a prevalence of 26.5% and this is consistent finding from a study that reported 27.2% and it is believed to be as a result of treatment with aminoglycosides amikacin, kanamycin and streptomycin.[37,40] Ototoxicity reported a prevalence of 6.2% and this is similar to studies done in Ethiopia and India which reported a prevalence of 4.8% and 10.12% respectively and it is also associated with the same drugs that cause hearing loss.[11,44]

Psychosis reported a prevalence of 1.5% and this is similar with a study that reported it as 1.4%[40] which is associated with the use of cycloserine. Arthralgia was reported to have a prevalence of 9.8% which is also in agreement to a study that reported 9.2% and is believed to be related to pyrazinamide use.[33] While this study reported vertigo to have a prevalence of 4.0% this was a similar finding in a study that reported a prevalence of 5%.[33] and this is attributed to the use of aminoglycosides for treatment. Renal dysfunction was seen to have a prevalence of 2.9% in this study and this is similar to 1.7% as reported in a study done in China.[41] Peripheral neuropathy was reported in 8.0 and this similar to a study that reported 5.04% prevalence.[33]

4.1 Patient-related factors associated with ADRs on DR-TB treatment

These factors include age: young or old age, while young people may not metabolize and eliminate drugs efficiently, older people may have other health issues and taking drugs that may react with or worsen the ADRs to RR/MDR-TB treatment. Also, as people age, the liver functionality decreases and is less able to metabolize and the kidney excretes drugs from the body. Concomitant use of other drugs is also a factor that affects the metabolism and excretion of drugs just like older age and the number and severity of ADRs rises unduly as the number of drugs increases. The use of alcohol, which is technically a drug may cause liver damage further increasing the risk of ADRs. Smoking may cause reactions to the drugs hence increasing the risk of ADRs.[39,40] Sex as a risk factor for developing ADRs is an important factor determining drug use and reactions, females are reported to have a greater risk of ADRs compared to males. In fact, older age and females are significantly associated with ADRs leading to hospitalizations.[40] Inherited factors can make some people more prone

to the toxic effects of certain drugs and certain diseases can alter absorption, metabolism, elimination and response to drugs.[40] Other factors are overweight/obesity, pregnancy, breastfeeding, anaemia, underweight, malnutrition, diabetes mellitus, HIV infection and hepatitis B or C co-infection.[39–41]

In comparing the ADRs reported by patients and clinicians (Figures 3 and 4), patients reported more ADRs while on the long regimen (Figure 3) compared to the short regimen. This may be from the fact that patients had more clinics visits while on long regimen thereby having more opportunities to report ADRs as they occur and also long regimen is known to be associated with more ADRs compared to short regimen. Clinicians reported hearing loss for the long-term regimen (Figure 4) this is probably because routine audiometry tests are done at the start of treatment and repeatedly during the course of the treatment. The association between hearing loss and duration of treatment with second line injectables was not covered in this study.

4.2 Discordance (disagreement) between patient self-report and clinician records of ADRs

ADRs were reported more by patient self-report than by the clinician record. Our finding for hearing loss (Kappa score 0.07, 95% CI -0.05 - 0.19; slight agreement) is not in agreement with a study that reported a high Kappa score of hearing loss. Hearing loss is typically measured objectively by audiometry, and clinician's base their findings on the audiology report.[46] Patients may under-report symptoms or ADRs during an interview. While the patient interview and file review asked about the 4 weeks prior to the interview, it may be that patients already experienced hearing loss prior to the 4 weeks and had not noticed any further deterioration so they did not report this in the interviews whereas clinicians use the audiometry results and would compare to previous visits and would therefore note smaller changes and document hearing loss (i.e., more sensitive than self-report).[46] Sometimes patients may not notice the hearing loss or those that experience hearing loss in the intensive phase do not notice a change/ worsening in their symptoms over time/rest of treatment. In this study questionnaires were administered in English and verbally translated into local languages by interviewers so a poor understanding of the questions could also contribute to reporting bias.

ADRs with the highest Kappa scores were psychosis (0.49) moderate, rashes (0.33) and joint pain/arthralgia (0.26) both were fair. In this study, the highest percentage of agreement were seen in psychosis and palpitation/tachycardia with 99% each followed by rashes and anaemia with 97% each, giving an almost perfect picture of agreement. This is suggesting that both patients and clinicians reported these ADRs almost equally and this is promising as prompt identification and management of these ADRs could help improve and enhance adherence and compliance to treatment resulting in improved patient outcomes. There seems to be better agreement when the ADRs are diagnoses than when they are signs and symptoms and clinicians seem to note that better. Poor discordance is noted with signs and symptoms. What the patient is experiencing may be used to make the diagnosis but the clinician is not reporting the sign or symptoms or the severity.

4.3 Association between missed clinicians' records of ADRs and missed clinic appointments.

We found that a missed clinician record of ADR was not associated with missing a subsequent scheduled clinic appointment. This finding is in contrast to the study that reported that missed diagnosis of ADRs results in poorer treatment outcomes.[17] A missed clinician record of ADR does not necessarily mean that the patient was not managed appropriately, but could rather suggest a reporting/documenting issue. And would possibly explain why patients are not at increased risk of missing a scheduled follow-up clinic visit (within 3 months of their interview date). It may also be possible that the outcome (within 3 months of their interview date) was measured too soon. In future work we plan to explore the effect of missed clinician record of sign/symptom or diagnosis on DR-TB treatment outcomes. Other studies have reported unfavorable ('death', 'loss to follow-up' (LTFU), 'failure' and 'not evaluated') treatment outcomes among MDR/RR-TB patients coupled with a high occurrence of serious adverse events in a predominantly HIV co-infected cohort, so it is possible that this is where we could observe an effect. In future work we could extend the study period and explore the association between missed clinician record of ADR over multiple consecutive visits and unfavorable treatment outcomes. RR/MDR-TB patients who miss appointments may not have been able to visit the clinic because of TB morbidity or mortality or adverse drug events, but clinicians are not able to intervene if the patient is not in the clinic.[53]

This study found that patients with rifampicin mono-resistant TB (sensitive to INH) were less likely to miss their subsequent scheduled visit compared to those with RIF by Xpert), this may be due to the fact that the treatment of RIH mono-resistant tuberculosis involves 9 – 12 months of shorter course regimen or a longer regular MDR-TB regimen of 18 – 20 months in a few cases using various second line anti-TB drugs, including an injectable drug for 4 – 8 months which are associated with heightened toxicity and cost.[65] ADRs are commonly reported during the intensive phase of treatment, so the longer patients remain on treatment, the more likely they are to remain in care. Patients initiating ART are more likely to experience an AE in the first six months of the DR-TB treatment.

4.4 Association between missed clinician record of ADRs and missed clinic appointments with a clinic visit, among patients that missed a clinic visit.

Unexpectedly, just over half of the patients who reported AEs had been receiving DR-TB treatment for more than 6 months. This could signify that either the AEs in the latter portion of DR-TB treatment are not as severe as those in the intensive phase and hence have lesser effect, or that these are persistent AEs that are either better tolerated or better managed than they had been during the intensive phase of treatment.[5]

4.5 Strengths

The strength of this study is that it is one of a few studies in South Africa to explore concordance between patient self-report and clinician record of ADRs during DR-TB treatment and the association between missed clinician record of ADRs and missed clinic appointments as a short-term outcome (Table 3.4). Methods used for this study helped to reduce the possibility of introducing bias. First, patients were asked about their symptoms/diagnosis (using a standardized questionnaire) in the 4 weeks prior to the interview date to reduce recall bias, then medical files were reviewed for the same period. Second, the researcher was blinded to the patient self-report of ADRs to DR-TB treatment until after the file review had been completed. Last, data for the cohort was from the electronic data information system. Data is entered by clinic staff (including visit data which was the primary outcome of the analysis) but is routinely checked by HE^{2}RO data staff for accuracy and completeness. This study used both patient self-report from interviews and clinician record from medical file review to capture ADRs to second line treatment of DR-TB.

4.5 Limitations

The limitations of this study could be discussed as firstly, the use of secondary data that is data not collected for this particular study as patients still in care/attending visits were enrolled, thus excluding patients that were sicker, had died, or may have more severe ADRs and were hospitalized during the study period. And no visit data for 49 patients which may therefore had overestimated the "missed clinician report of ADRs" (because we had the patient self-report but no notes in the patient file to compare to). The sample size was also small which may affect the reliability of the results because it leads to a higher variability, which may lead to bias.

Secondly, the study design used in this study is cross-sectional and it has limitations such as inability to determine temporality and causality. The preferred study design for this would be a prospective study, where the symptoms (patient self-report) and diagnosis (clinicians record), are collected at the same time and then patients are followed up to see if they experience a poorer outcome (missed visit). This study is quantitative and did not include qualitative interviews with patients to understand the patient's experience.

Thirdly, HIV rates of HIV co-infection (78%) in this cohort and overlapping toxicities from DR-TB treatment and ART make it difficult to tease out ADRs from RR/MDR-TB treatment versus those from ART.

Fourthly, most of the study participants were on long course treatment and very few (16%) were on short course treatment so it was difficult to disentangle ADRs from long term and short-term treatment.

Lastly, the data for this study was collected from only one of the decentralized outpatient facilities in Gauteng province providing integrated TB and HIV care, therefore the generalizability of the findings of this study may be limited to this study population.

CHAPTER 5

5.0 Conclusion and Recommendations

5.1 Conclusion

Discordance between patient self-report and clinician report of ADR is likely to occur as symptoms reported by patients may not be recorded by clinicians due to heavy work load. Knowing which ADRs to consider acceptable to patients while on the treatment is also important. Communication barrier as a result of the differences in the level of education of patients and clinicians can also lead to discordances in reporting of ADRs. Early detection, prompt management and pharmacovigilance reporting of ADRs remain key factors in the management of RR/MDR-TB.

5.2 Recommendations

From the findings of this study, recommendations are made on the regular training and retraining of patients and on how to identify and report ADRs to RR/MDR-TB treatment. Periodic training and retraining of clinicians on the prompt identification and management of ADRs is also a way of achieving patients' adherence to clinic visits and adherence to medications which is aimed at improved treatment outcomes. Adjusting the work load on clinicians attending to RR/MDR-TB patients at clinics will help give the clinicians ample time with each patient to identify ADRs as reported by the patients to avoid discordances. Joint reporting of ADRs from patients in a checklist method for their appointment with the clinician may help to improve clinical management and patient satisfaction with treatment. Inclusion of patient's reports into clinicians reporting of ADRs will support active pharmacovigilance programmes aimed at improving patient treatment outcomes.[46] Continuous education of patients on the dangers of missed clinic appointments will improve attendance at clinics, adherence to treatment and ensure prompt reporting and management of ADRs resulting in overall improved treatment outcomes. Also, establishment of policies relating to reporting of ADRs during TB and RR/MDR-TB treatment by both clinicians and patients, improvement and closer relationship between clinicians and pharmacovigilance centres will go a long way to further help. There is also a call for standardization of the reporting of ADRs so that the results can be compared across other cohorts and settings. Clinicians should report the signs, symptoms and severity continuously at each visit to see if

they are persistent or resolving over time. Patient satisfaction with treatment can also be assessed if their signs, symptoms and severity are asked about over time.

5.3 Suggestions for further studies

Being that this study is one of the few studies looking at the discordance between patient self-report of ADR and clinicians record of ADRs to RR/MDR-TB treatment and the association between missed clinician record of ADRs and missed clinic appointments, there is paucity of data in these areas suggesting a need for further studies.

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5.5 Conflict of interest

The authors declare no conflict of interest in this study

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APPENDICES

Appendix A: Plagiarism Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

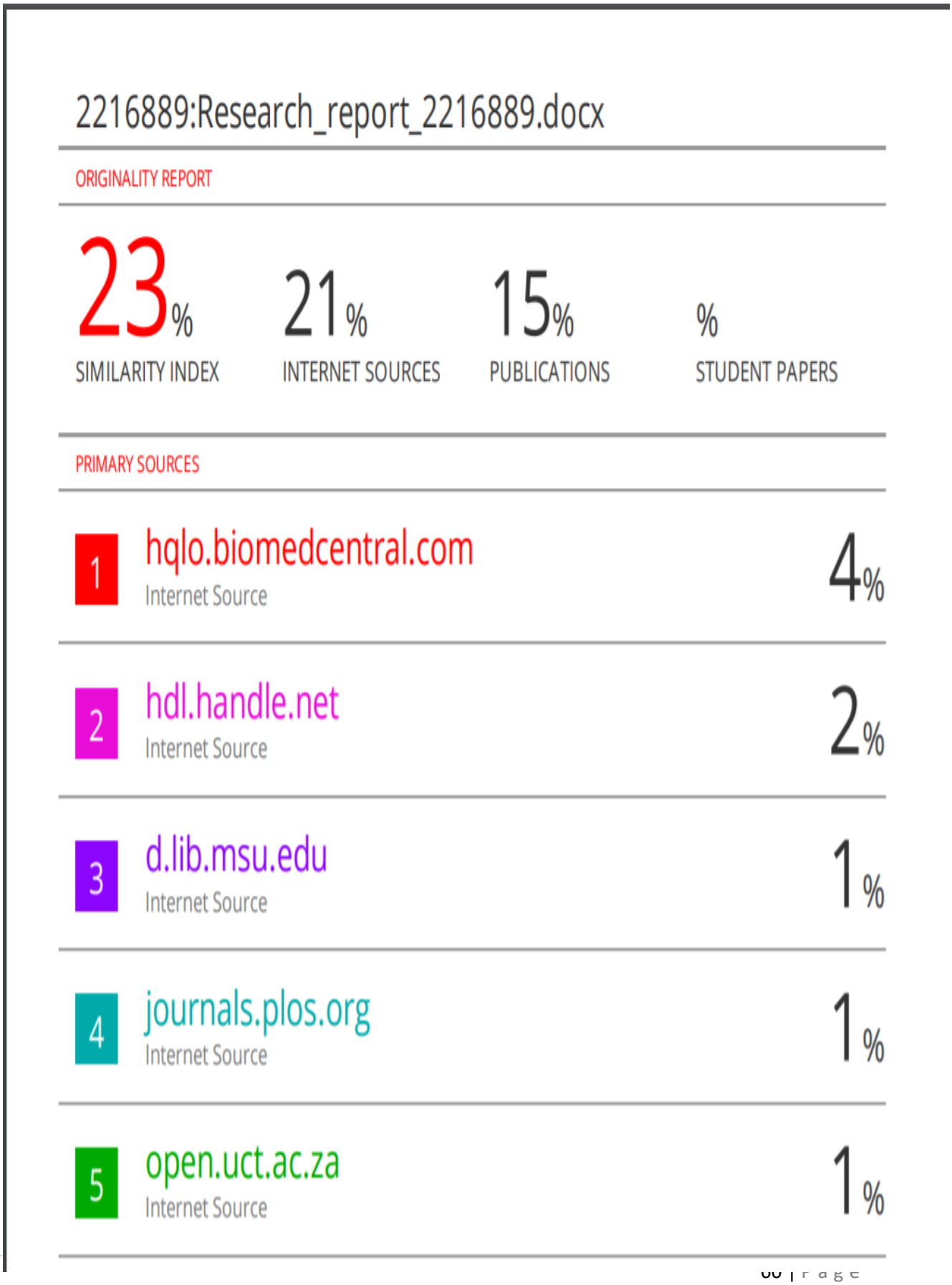
I ,Unyime Abasiodiong Iniobong (Student number: 2216889) am a student registered for the degree of MSc. Epidemiology and Biostatistics in the academic year 2019.

I hereby declare the following:

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

Signature: _____ Date: 20th October, 2021.

Appendix B: Turnitin Report



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Appendix C: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr D Evans
Wits Health Consortium
Health Economics and Epidemiology Research Office
39 Empire Road
Parktown
Johannesburg

E-mail: devans@hero.za.org

CC: Supervisor: Not applicable <>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/03/25

REF: *R14/49*

PROTOCOL NO: **M200380** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Quality of life and adverse event surveys amongst a cross-section of drug-resistant TB patients at the Helen Joseph Hospital, Johannesburg, South Africa*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix D: Table showing the patients clinical characteristics, categories, and their definitions.

Variable	Categories	Definition
Resistance pattern	MDR-TB (RIF and INH resistant) RIF resistant by Xpert MTB/RIF RIF mono-resistant (INH sensitive)	This was categorized according to the diagnostic methods used: rifampicin (RIF) resistant by Xpert MTB/RIF, MDR-TB (RIF and isoniazid resistant), or RIF mono-resistant (mono- or poly-resistance to RIF alone or RIF plus another first-line drug except isoniazid, confirmed by line probe assay or DST).
HIV status	HIV negative HIV positive HIV positive on ART HIV positive not on ART Unknown	This was categorized according to the HIV results recorded in the patient file. Unknown were those patients without HIV results recorded in the file.
Duration of ART treatment	≤ 6 months >6 months Missing	This was estimated from the time of start of treatment till the date of interview. Missing were those patients without the date of start of treatment recorded in file.
Duration of DR-TB treatment	≤ 6 months >6 months	This was estimated from the time of start of treatment till the date of interview.
DR-TB regimen	Standard long course Individualized long-course Standard short course Individualized short course	This was categorized as regimen taken as at the time of interview into standard or individualized (that is substituted for kanamycin) long or short course regimen.
Baseline CD4count	< 50 cells/mm^3 51 – 250 cells/mm^3 >250 cells/mm^3	This was categorized based on the most current result of CD4 test at the time of interview.
Patient category	New Previously treated Missing	This was categorized based on the information gotten at the time of interview whether patient was new to DR-TB treatment or have been on the treatment before. Missing were those patients without records of this.
TB type	PTB and EPTB or EPTB only PTB and not reported.	This was categorized based on the site of the TB infection: PTB (TB in the lungs) Extra pulmonary TB (EPTB) TB outside the lungs.
Smear microscopy	Negative Positive	This was categorized based on the result of sputum smear microscopy at the time

	Unknown	of interview. Unknown were those patients without results recorded.
Diabetes	No Yes Missing/unknown	This was categorized based on the results of the blood sugar test recorded in the patients file at the time of initiation of treatment. Missing/unknown were those patients without any results.
Weight	< 50 kg >50kg Missing	This was categorized based on weight recorded in the patients file at the time of initiation of treatment.
Referring facility	Outpatient Inpatient	This was categorized based on the method of referral to the TB clinic. Outpatient were patients that were referred from outside hospital. Inpatient were patients that were referred from other departments of the hospital.
Anaemia	None or mild (Hb ≥11.0g/dl) Moderate (8 -10.9g/dl) or Severe (<8 g/dl) Missing	In defining anaemia, haemoglobin (Hb) was adjusted downward by 0.65 g/dl taking into consideration that Johannesburg is above sea level.[66]. This was categorized based according to WHO guidelines as none (Hb ≥12g/dl for non-pregnant women and Hb ≥13g/dl for men), moderate (8 -10.9g/dl) and severe (Hb <8g/dl).[43] Missing were those patients without any records on this.

Appendix E: Table showing re-classification of clinicians record of ADRs is affected by laboratory results and concomitant medications.

Adverse drug reactions	Total number (N = 149) (n/N, %)	Patient self-report (n/N, %)	Clinician record (n/N, %)	Re-classification: Clinician report + Laboratory results + Concomitant medication
Hearing loss	73 (48.9)	15 (10.1)	58 (38.9)	
Psychosis	4 (2.7)	2 (1.3)	2 (1.3)	
Peripheral Neuropathy	22 (14.8)	16 (10.7)	6 (4.0)	
Rashes	6 (4.0)	5 (3.4)	1 (0.7)	3
Vomiting	13 (8.7)	12 (8.1)	1 (0.7)	3
Nausea	14 (9.4)	12 (8.1)	2 (1.3)	
Anemia	4 (2.7)	1 (0.7)	3 (2.0)	32
Joint pain /Arthralgia	27 (18.1)	22 (14.8)	5 (3.4)	22

Palpitation /Tachycardia	2 (1.3)	1 (0.7)	1 (0.7)	
Diarrhea	2 (1.3)	2 (1.3)	0 (0)	5
Abdominal pain	2 (1.3)	2 (1.3)	0 (0)	
Myalgia	10 (6.7)	10 (6.7)	0 (0)	
Visual disturbance	4 (2.7)	4 (2.7)	0 (0)	
Vertigo	11 (7.3)	11 (7.4)	0 (0)	
Depression	9 (6.0)	9 (6.0)	0 (0)	1
Headaches	2 (1.3)	2 (1.3)	0 (0)	10
Insomnia	2 (1.3)	2 (1.3)	0 (0)	
Fatigue	6 (4.0)	6 (4.0)	0 (0)	
Ototoxicity	17 (11.4)	0 (0)	17 (11.4)	
Poor appetite	1 (0.7)	0 (0)	1 (0.7)	
Renal dysfunction	8 (5.3)	0 (0)	8 (5.4)	12
Hypothyroidism	14 (9.4)	0 (0)	14 (9.4)	
Hyperthyroidism	1 (0.7)	0 (0)	1 (0.7)	
Gynecomastia	2 (1.3)	0 (0)	2 (1.3)	
Non-Hodgkin's lymphoma	2 (1.3)	0 (0)	2 (1.3)	
Skin toxicity	1 (0.7)	0 (0)	1 (0.7)	
Renal toxicity	5 (3.4)	0 (0)	5 (3.4)	9
Weight gain	1 (0.6)	0 (0)	1 (0.7)	
Weight loss	1 (0.6)	0 (0)	1 (0.7)	
Liver toxicity	1 (0.6)	0 (0)	1 (0.7)	3
Liver dysfunction	1 (0.6)	0 (0)	1 (0.7)	3
Pancytopenia	1 (0.6)	0 (0)	1 (0.7)	
Gout	1 (0.6)	0 (0)	1 (0.7)	
Allergy	1 (0.6)	0 (0)	1 (0.7)	
Tinnitus	2 (1.3)	0 (0)	2 (1.3)	
Epilepsy	2 (1.3)	0 (0)	2 (1.3)	

Appendix F: Table showing the division of ADRs into symptoms and diagnosis.

Symptoms	**Diagnosis**
Nausea	Psychosis
Vomiting	Peripheral neuropathy
Rashes	Anaemia
Hearing loss	Vertigo
Joint pains	Arthralgia
Palpitations	Tachycardia
Diarrhoea	Gynaecomastia
Abdominal pains	Depression
Headaches	Ototoxicity
Fatigue	Renal dysfunction
Poor appetite	Renal toxicity
Weight gain	Hyperthyroidism

Weight loss	Hypothyroidism
Allergy	Non–Hodgkins lymphoma
Tinnitus	Skin toxicity
Insomnia	Liver toxicity
	Liver dysfunction
	Pancytopenia
	Gout
	Epilepsy
	Visual disturbances

Appendix G: Table showing proportion of patient reports of ADRs by treatment regimen.

Patient self-reports of ADRs	**Treatment regimen**		
	Long course N (%)	Short course N (%)	Total
No	78 (62.40)	13 (54.17)	91
Yes	47 (37.60)	11 (45.83)	58
Total	125	24	149

Appendix H. Characteristics of patient that had a clinic visit in the 4 weeks preceding the interview date compared to those that did not.

	Total N = 149 n (%)	Clinic visit N = 83 n (%)	No clinic visits N = 66 n (%)	P value**
At start of DR-TB treatment				
Sex				
Male	82 (55.00)	46 (56.10)	36 (43.90)	0.915
Female	67 (45.00)	37 (55.22)	30 (44.78)	
Age at treatment initiation (years)				
18 - 35	74 (49.70)	37 (50.00)	37 (50.00)	0.164
>35	75 (50.30)	46 (61.33)	29 (38.67)	
Employment status				
Unemployed	85 (57.0)	50 (58.82)	35 (41.18)	0.331
Employed	63 (42.3)	33 (50.79)	31 (49.21)	
Missing / Unknown	1 (0.70)	0 (00.00)	0 (00.00)	
Education				
Primary school or no education	14 (9.40)	9 (64.29)	5 (35.71)	0.702
Secondary school and high school	113 (75.8)	63 (55.75)	50 (44.25)	
Higher than matriculation	22 (14.7)	11 (50.00)	11 (50.00)	
Resistance pattern				
MDR-TB (RIF and INH)	32 (21.5)	26 (68.42)	12 (31.58)	0.154
RIF resistant by Xpert MTB/RIF	38 (25.5)	35 (52.24)	32 (47.76)	
RIF mono-resistant (INH sensitive)	67 (45.0)	18 (56.25)	14 (43.75)	
Missing	12 (8.1)	4 (33.33)	8 (66.67)	
HIV status*				
HIV negative	27 (18.1)	13 (48.15)	14 (51.85)	0.463
HIV positive	116 (77.9)	57 (60.64)	37 (39.36)	
HIV positive and on ART	94 (81.0)	10 (45.45)	12 (54.55)	
HIV positive not on ART	22 (19.0)	3 (50.0)	3 (50.0)	
Unknown	6 (4.0)	0 (00.00)	0 (00.00)	
DR-TB regimen				
Standard long-course	92 (61.7)	57 (61.96)	35 (38.04)	0.281
Individualized long-course	33 (22.2)	15 (45.45)	18 (54.55)	
Standard short-course	15 (10.1)	7 (46.67)	8 (53.33)	
Individualized short-course	9 (6.0)	4 (44.44)	5 (55.56)	
Diabetes				
No	109 (73.2)	64 (58.72)	45 (41.28)	0.231
Yes	6 (4.0)	5 (83.33)	1 (16.67)	
Missing	34 (22.8)	14 (28.89)	20 (38.15)	
Anaemia				
None or mild (Hb ≥11.0g/dl)	64 (43.0)	36 (56.25)	28 (43.75)	0.116
Moderate (8-10.9g/dl)	26 (17.5)	10 (38.46)	16 (61.54)	
Missing	59 (39.6)	37 (62.71)	22 (37.29)	
Weight at treatment initiation (kg)				
<50	37 (24.8)	61 (59.22)	42 (40.78)	0.422
≥50	103 (69.1)	18 (48.65)	19 (51.35)	
Missing	9 (6.0)	4 (44.44)	5 (55.56)	
TB type				
PTB only/PTB with EPTB	131 (87.9)	4 (57.14)	3 (42.86)	0.776
EPTB	11 (7.3)	74 (56.49)	57 (43.51)	

Unknown	7 (4.7)	5 (45.45)	6 (54.55)	
Smear microscopy				
Negative	99 (66.4)	61 (61.62)	38 (38.38)	**0.016**
Positive	26 (17.5)	15 (57.69)	11 (42.31)	
Unknown	24 (16.1)	7 (29.17)	17 (70.83)	
Referring facility				
Outpatient	100 (67.1)	59 (59.00)	41 (41.00)	0.247
Inpatient	49 (32.9)	24 (48.98)	25 (51.02)	
Patient category				
New	90 (60.4)	48 (53.33)	42 (46.67)	0.281
Previously treated	36 (24.2)	24 (66.67)	12 (33.33)	
Missing	23 (15.4)	11 (47.83)	12 (52.17)	
At interview date				
Duration on DR-TB treatment (months)				
≤6	66 (44.3)	31 (46.97)	35 (53.03)	0.056
>6	83 (55.7)	52 (62.65)	31 (37.35)	
Duration on ART treatment (months)				
≤6	14 (14.9)	9 (64.29)	5 (35.71)	0.512
>6	67 (71.3)	42 (62.69)	25 (37.31)	
Missing	13 (13.8)	6 (46.15)	7 (53.85)	

*Among those who were HIV positive (n = 116); Hb haemoglobin, EPTB extra pulmonary TB, PTB pulmonary TB, ADR adverse drug reaction, RIF rifampicin, INH isoniazid. **Proportions were compared across those that had a clinic visit and those that did not using the chi-square test for proportions (or Fisher Exact test for sparse data). Bold font p<0.05.

Appendix I. Aerial view of Helen Joseph hospital in Johannesburg, South Africa.

Appendix J. Certificate of examination submission by the candidate.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

CERTIFICATE OF SUBMISSION FOR EXAMINATION OF MASTERS RESEARCH REPORT / DISSERTATION OR PHD THESIS SIGNED BY HIGHER DEGREES CANDIDATES

Full name	Unyime Abasiodiong Iniobong
Student number	2216889

Title of submitted Research Project: Discordance Between Patient Self-report and Clinician record of Adverse Drug Reaction to Drug Resistant Tuberculosis Treatment in Johannesburg, 2015 - 2018

NB: If this title is different to your previously approved title, no further action can be taken by the Faculty Office until a change of title has been approved.

Contact no	+234 7065203499	E-mail	2216889@students.wits.ac.za

1. If you are likely to move in the next 6-12 months, please give the anticipated date of move: _____
2. I hereby submit my **Masters (research report) / Masters (dissertation) / PhD thesis for examination** (Select whichever is applicable)
3. I have checked all copies of my research report / dissertation / thesis and declare that no pages are missing or poorly reproduced.
4. I have submitted _____ bound copies and _____ copies on CD

5. **I confirm that I have:**
   a) A signed declaration indicating my understanding of the concept of plagiarism and a denial of plagiarism in my research document.
   b) A report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document included as an appendix.

6. **I confirm that I have:**
   a) Not used either human or animal tissue or records **Yes/No**
   b) If yes: I have included the ethics waiver letter pertinent to my research as an appendix **Yes/No**
   c) Done research using animals **Yes / No**
      If yes: I have included a copy of the animal ethics committee clearance certificate as an appendix in this document **Yes/No**
   d) Done research using human subjects, human tissue or patient records **Yes / No**
      If yes: I have included a copy of the human ethics clearance certificate as an appendix to the research document **Yes/No**

7. I understand that I may not graduate unless my university fees have been paid in full.
8. My supervisor(s) names, departments, telephone numbers and email addresses are as follows:

Name	Dr. Denise Evans		
Department	Health Economics and Epidemiology Research Office.		
Telephone	+27 (0) 10 001 0637	E-mail	devans@heroza.org
Name	Ms. Tembeka Sineke		
Department	Health Economics and Epidemiology Research Office.		
Telephone	+27 (0) 10 001 2942	E-mail	tsineke@heroza.org
Name			
Department			

Telephone		E-mail	

List all publications, which you have published in peer-reviewed journals from your postgraduate research report/dissertation/thesis during the course of your studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

Nil

_____ Date: 20th October, 2021.