ADVERSE DRUG REACTIONS AND RESULTANT HEALTH-RELATED QUALITY OF LIFE DURING MULTIDRUG-RESISTANT TUBERCULOSIS TREATMENT IN SOUTH AFRICA

By

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ABSTRACT

ADVERSE DRUG REACTIONS AND RESULTANT HEALTH-RELATED QUALITY OF LIFE DURING MULTIDRUG-RESISTANT TUBERCULOSIS TREATMENT IN SOUTH AFRICA

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Background/Significance: The incidence of multidrug-resistant tuberculosis (MDR-TB) is on the rise globally. MDR-TB takes a minimum of 2 years to treat and the treatment regimen produces many adverse drug reactions (ADRs). The World Health Organization (WHO) has called for further research on the treatment of community-based MDR-TB patients as care is being decentralized to outpatient settings. In the WHO's TB progress report for 2015, they note there is a dearth of literature about anti-TB drug-induced mortality, morbidity and loss in quality of life, particularly in low-resource settings. **Purpose:** This study directly addresses this gap in knowledge by examining the effect of ADRs from MDR-TB treatment on heath-related quality of life (HRQOL) for patients in a low-resource, high HIV-burden population in South Africa. **Methods:** A cross-sectional, observational study design was used to: 1) describe patient and clinical characteristics of community-based MDR-TB patients; 2) examine the relationship between Aim 1 characteristics and ADRs; and 3) examine the effect of each ADR on HRQOL, controlling for Aim 1 characteristics. MDR-TB patients in the initial intensive phase of treatment were recruited using convenience sampling from an outpatient MDR-TB clinic in South Africa. Patient interviews were conducted in English

or *isi*Zulu and included questions on individual characteristics (age, sex, education, employment, relationship status, alcohol/smoking, stigma, and adherence) and environmental characteristics (housing status, food insecurity, social support and discrimination). ADRs and symptom bother over the past month of treatment were collected using a symptom checklist and HRQOL was collected using the EQ-5D. A medical chart data abstraction was conducted to capture MDR-TB treatment, HIV/AIDS status and treatment, co-morbidities, BMI, and laboratory values. **Results:** Aim 1: The majority of participants (*n*=121) were co-infected with HIV (75%), female (51%), and did not have enough food to eat everyday (51%). Aim 2: All but two participants reported at least one ADR (98%) with an average of 8.6 per person. In the multivariable analysis, being female and starting MDR-TB treatment with elevated liver enzymes were significantly related to an increase in total ADRs. There was no significant difference in ADRs by HIV status. Aim 3: An increase in total ADRs was significantly related to a decrease in HRQOL. Of the 18 ADRs assessed, six were associated with a decrease in HRQOL in the final model: tinnitus, gastrointestinal symptoms: nausea/vomiting and diarrhea, and symptoms affecting movement: myalgia, arthralgia, and peripheral neuropathy. Patient and clinical characteristics that remained significant were the loss of relationship and hospitalization during treatment, with past hospitalization associated with increased HRQOL. **Implications:** This study helps fill the knowledge gap on the effect of ADRs from MDR-TB treatment on HRQOL. For clinicians, findings reinforce the need to improve detection, documentation and management of ADRs. Further research is needed to determine effective ADR management techniques to improve HRQOL outcomes for patients on this lengthy and challenging treatment.

Dedicated to my parents for their unwavering support

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

ALT	Alanine transaminase
ART	Anti-retroviral therapy
BMI	Body Mass Index
EFV	Efavirenz
EMB	Ethambutol
EQ-5D	EuroQOL five dimension
EQ-VAS	EuroQOL visual analogue scale
Eto	Ethionamide
FTC	Emtricitabine
GI	Gastrointestinal
Hgb	Hemoglobin
HRQOL	Health-related quality of life
INH	Isoniazid
IRB	Institutional Review Board
K	Potassium
KDH	King Dinuzulu Hospital
Km	Kanamycin
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
MSU	Michigan State University
MMAS-8	Morisky Medication Adherence Survey 8-item

MT-SI	MDR-TB Treatment Symptom Index
NHLS	National Health Laboratory Service
PAS	Para-aminosalicylic acid
PI	Principal investigator
PZA	Pyrazinamide
RA	Research assistant
REDCap	Research Electronic Data Capture
RIF	Rifampicin
RSA DOH	Republic of South Africa Department of Health
SES	Socioeconomic status
TB	*Mycobacterium tuberculosis*
TDF	Tenofovir
TSH	Thyroid stimulating hormone
Tz	Terizidone
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

CHAPTER 1: Background and Significance

Background of Study

Mycobacterium tuberculosis (TB) is the primary cause of mortality in South Africa (Statistics South Africa, 2013) and is the leading cause of death in persons living with HIV/AIDS globally (World Health Organization [WHO], 2015b). South Africa has the highest incidence of TB in the world (860 cases per 100,000 population) (WHO, 2014c) and the highest number of persons living with HIV (WHO, 2013), with more than 60% of TB cases also co-infected with HIV (WHO, 2014c).

The clinical picture of TB/HIV co-infection is further complicated by the rising incidence of multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to the most powerful first-line anti-TB medications, isoniazid (INH) and rifampicin (RIF). MDR-TB requires treatment with second-line anti-TB therapy, which is less effective and more toxic than the first-line medications (WHO, 2014a). Treatment lasts a minimum of 24 months, compared to six months for drug-susceptible TB and requires a minimum of five medications. Second-line anti-TB therapy is known to cause a variety of significant physical and mental adverse drug reactions (ADRs) and has many shared toxicities with HIV treatment (Scano et al., 2008; WHO, 2014a).

Globally, treatment success rates for MDR-TB remain alarmingly low, around 50% (WHO, 2014c), with similar outcomes in South Africa (Cox et al., 2014; Farley et al., 2011). The WHO has called MDR-TB a major health problem, with fears of a worsening global epidemic as mismanaged MDR-TB has led to reported cases of more resistant strains of MDR-TB, known as extensively drug-resistant tuberculosis (XDR-

TB), in 100 countries, including all countries in North America and most in Europe (WHO, 2014c).

Multidrug-Resistant TB (MDR-TB)/HIV Co-Infection in South Africa

There were half a million estimated new cases of MDR-TB globally in 2013 (WHO, 2014c), with numbers in South Africa increasing steadily since 2006 (Republic of South Africa Department of Health [RSA DOH], 2013a). In 2010, there were 7386 confirmed cases of MDR-TB in South Africa, with the largest proportion of cases (27.5%) in KwaZulu-Natal province. The number of patients diagnosed with MDR-TB far exceeds the number of available hospital beds, particularly in KwaZulu-Natal. Therefore, the South African DOH has begun decentralizing the care of MDR-TB patients into the community (RSA DOH, 2013a). Community-based, or outpatient, MDR-TB treatment has been effective in low HIV-burden countries, such as Peru (Shin et al., 2004) and Nepal (Malla et al., 2009), but South Africa has the added challenge of almost 70% HIV co-infection, which requires rapid anti-retroviral therapy (ART) initiation based on current WHO recommendations (RSA DOH, 2013b; WHO, 2014b). Initial community-based treatment outcomes in South Africa have been promising (Brust et al., 2012; Loveday et al., 2015), but there is a great need for further research on the response to MDR-TB treatment in a community setting with the added burden of a high rate of HIV co-infection.

Adverse Drug Reactions (ADRs) During MDR-TB treatment

Adverse drug reactions are common during MDR-TB treatment, with other studies conducted in sub-Saharan Africa reporting 80%-99% incidence of at least one ADR (Bezu, Seifu, Yimer, & Mebrhatu, 2014; Brust et al., 2013; Jacobs & Ross, 2012;

Mpagama et al., 2013; Sagwa, Mantel-Teeuwisse, & Ruswa, 2014; Seung et al., 2009). Further, a recent meta-analysis of 5346 MDR-TB patients worldwide found that 70.4% ADR cases required a change to the MDR-TB treatment regimen (Wu et al., 2013).

The classic definition of an ADR is "a response to a drug that is noxious and unintended and occurs at doses normally used" (WHO, 1972). This study utilizes an updated definition of an ADR as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards & Aronson, 2000, p. 1255). This definition removes minor unwanted reactions, as the reaction must be "appreciably" unpleasant or harmful enough for the patient and/or the healthcare provider to consider the ADR problematic. The terms ADRs and side effects are synonymous except that ADRs only include the unintended negative responses to the medication, whereas side effects could also encompass unintended beneficial effects (Edwards & Aronson, 2000). For this reason, the term ADR is preferable to side effect. Adverse drug reactions encompass both signs (objective clinical or laboratory evidence such as an increased creatinine level) and symptoms (subjective evidence such as nausea), with symptoms being the way the patient personally experiences the ADRs (Justice et al., 2001).

This study focuses on the common ADRs listed in the most recent WHO MDR-TB guidelines (WHO, 2014a). These include 18 ADRs, which can be analyzed by body system, but should be recorded individually. Gastrointestinal (GI) ADRs are usually the most common (Nathanson et al., 2004; Wu et al., 2013): 1) nausea/vomiting, 2)

diarrhea, 3) anorexia and 4) gastritis/abdominal pain. Ototoxic effects refer to ADRs that result from damage to cranial nerve VIII, the vestibulococchlear nerve, which can manifest as: 5) loss of hearing, 6) tinnitus, 7) dizziness or vertigo. Musculoskeletal effects include: 8) myalgia and 9) arthralgia. Dermatological effects include: 10) rash or pruritis. The nervous system ADRs are the most variable as the peripheral nervous system can be affected through: 11) peripheral neuropathy or 12) visual disturbance, most notably from optic neuritis. The central nervous system effects may include: 13) headaches, 14) insomnia, 15) fatigue, or 16) confusion, or as a psychiatric disorder including: 17) depression or 18) anxiety.

In addition, there are four ADRs that can normally only be assessed through laboratory findings. These include electrolyte wasting, most notably through decreased potassium (K), hepatotoxicity defined by an elevated alanine transaminase (ALT), nephrotoxicity defined by an elevated creatinine level, and hypothyroidism defined by an elevated thyroid stimulating hormone (TSH) level (WHO, 2014a). Central nervous system effects may also progress to psychosis or seizure.

The majority of ADRs occur in the first of the two phases of MDR-TB treatment known as the intensive phase (Bloss et al., 2010; Isaakidis et al., 2012; Shin et al., 2007), with the earliest median time from treatment initiation to onset of first ADR documented at 21 days (Baghaei et al., 2011). The intensive phase, spanning at least the first 6 months of treatment, is defined by the administration of an injectable aminoglycoside agent, given once per day, five days a week. The length of the intensive phase is determined by adding four more months of the injectable agent to the date of the specimen collection for the first sputum culture conversion (RSA DOH,

2013a). The continuation phase, spanning at least an additional 18 months of treatment, follows completion of the injectable agent by continuing with the same oral medications.

The South African DOH follows a standardized regimen outlined by the WHO for MDR-TB treatment with weight-based dosing (RSA DOH, 2013a; WHO, 2014a). Kanamycin (Km) is the most commonly used injectable aminoglycoside agent in South Africa. The following oral medications are given for the entire length of the treatment: moxifloxacin (Mfx) (fourth-generation fluoroquinolone), pyrazinamide (PZA) and ethambutol (EMB) (the two remaining first-line anti-TB drugs), and ethionamide (Eto) and terizidone (Tz) (two bacteriostatic agents). In addition, all MDR-TB patients co-infected with HIV are eligible for ART irrespective of CD4 count, since TB is considered an AIDS-defining illness. The standardized ART regimen from the South African DOH is a once-a-day single pill of three combined medications: efavirenz (EFV) (a non-nucleoside reverse transcriptase inhibitor), tenofovir (TDF) and emtricitabine (FTC) (both nucleoside reverse transcriptase inhibitors) (RSA DOH, 2014).

Even though the presence of ADRs from MDR-TB treatment has been well documented in the literature, there has been great variability in the incidence of each ADR reported. For example, among two MDR-TB studies documenting the incidence of serious ADRs, one study reported 6.9% occurrence of at least one ADR (Van der Walt et al., 2013), while the other reported 100% (Furin et al., 2001). This heterogeneity of reporting may be challenging for clinicians to interpret. Potential causes of the variability in ADR incidence might include differences in study design (i.e., prospective vs. retrospective), differences in ADR definitions and groupings by body system and

differences in clinical recording practices. Concerning these differences, a study in India urgently called for data to better understand the patterns and risks of ADRs occurring among MDR-TB/HIV co-infected patients (Isaakidis et al., 2012). One of the aims in the current study is to help fill this gap in knowledge by providing data not only on the frequency of ADRs, but also on patient and clinical characteristics that may affect the frequency of the ADRs.

While nausea/vomiting is the most common ADR symptom (14% - 100%), ADRs affecting the nervous system, such as hearing loss (6.7% - 38.9%), psychosis (3.4% - 16%), and peripheral neuropathy (3% - 51%) may be irreversible and frequently require a change to the MDR-TB treatment regimen (Furin et al., 2001; Isaakidis et al., 2012; Nathanson et al., 2004; Seung et al., 2009; Törün et al., 2005; Van der Walt et al., 2013). Clinicians face a daunting task. As the MDR-TB regimen is already a second-line therapy due to resistance to the first-line TB treatment, clinicians, until recently, have very few replacement options and risk poor treatment outcomes if a medication must be removed due to an ADR (Masjedi et al., 2008). Yet, remaining on treatment while experiencing ADRs may lead to irreversible damage (Padayatchi, Daftary, Moodley, Madansein, & Ramjee, 2010; Sturdy et al., 2011). Newer regimens are slowly becoming available in South Africa, however, while improvements in treatment outcomes are expected, new ADR profiles present additional challenges (Diacon et al., 2014).

Effect of MDR-TB Treatment on HRQOL

Early detection and management of ADRs is essential for successful MDR-TB treatment, while limiting the negative impact on the patient's quality of life. Health-

related quality of life (HRQOL), defined as “the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment, or policy” (Patrick & Erickson, 1993, p. 419), provides a more focused measure of quality of life. Health-related quality of life is a multi-dimensional, patient-centered outcome that includes both physical health and mental health domains and can be seen as a trade-off between the length and quality of an individual’s life (Patrick, 1997).

Providers are often unaware of patient symptoms or may discount the symptoms of which they are aware (Edelman, Gordon, & Justice, 2010; Justice et al., 2001; Justice et al., 1999). While physiologic measures are of great importance to clinicians, they are often of less interest to patients and do not always correlate with a patient’s HRQOL (Guyatt, Feeny, & Patrick, 1993). Most studies in MDR-TB populations to date have categorized severity of ADRs by whether or not the ADR required a medical regimen change or put the patient at risk for death (Baghaei et al., 2011; Carroll et al., 2012; Datta et al., 2009). Yet, symptoms that are not associated with mortality may still be very bothersome to the patient and affect HRQOL or adherence (Corless, Nicholas, Davis, Dolan, & McGibbon, 2005). Patient-reported outcomes are defined as a report on the patient’s health status that comes directly from the patient without interpretation from the clinician (Food and Drug Administration, 2009; Simpson et al., 2013). This study examined MDR-TB patient-reported outcomes of ADRs including symptoms, degree of symptom bother and the effect on HRQOL to supplement more objective clinical signs, such as laboratory reports.

Significance of Study

While much research has been done separately on the HRQOL for persons with HIV and less in persons with drug-susceptible TB, very little has been written about HRQOL in the MDR-TB population or the MDR-TB/HIV co-infected population. A study of patients with susceptible TB, HIV, TB/HIV or MDR-TB in Thailand found that the patients with the lowest HRQOL were those with MDR-TB (Kittikraisak et al., 2012). Numerous studies in the past five years have cited a lack of HRQOL work in TB patients (Aggarwal, 2010; Babikako, Neuhauser, Katamba, & Mupere, 2010; Guo, Marra, & Marra, 2009). In the WHO's progress report outlining goals for 2015 in the treatment of MDR-TB, the authors note "there is a dearth of literature about anti-TB drug-induced mortality, morbidity and loss in quality of life, particularly in low-resource settings" (WHO, 2011, p. 17). This study directly addresses this gap in knowledge by providing much-needed data on HRQOL for MDR-TB patients in a low-resource, high HIV-burden population during the intensive phase of MDR-TB treatment.

This study provides an original contribution to science by determining which ADRs, patient variables, and clinical variables are associated with a lower HRQOL score during MDR-TB treatment. This is one of the first studies in an MDR-TB population with a high prevalence of HIV co-infection to provide a quantitative analysis of ADRs with a focus on patients' perceptions of symptoms by including symptom bother, thus providing a more patient-centered analysis of MDR-TB treatment to guide nursing care.

Specific Aims

Aim 1. To describe the individual and environmental patient and clinical

characteristics of community-based MDR-TB patients

Patient and clinical characteristics based on the MDR-TB Treatment HRQOL model (presented in Chapter 2) will be summarized and stratified by HIV status.

Aim 2. To examine the relationship between Aim 1 (patient and clinical) characteristics and ADRs, including signs, symptoms, and symptom bother

Relationship between the patient and clinical characteristics in Aim 1 and total ADRs will be examined to find potential explanatory variables associated with an increase in ADRs.

Aim 3. To examine the effect of each ADR on HRQOL, controlling for characteristics listed in Aim 1 as potential confounders

A multivariable linear regression model will be constructed to determine which ADRs have a statistically significant effect on HRQOL, while controlling for patient and clinical characteristics identified in Aim 1.

Hypothesis: A higher number of total ADRs and ADRs with higher symptom bother will be associated with lower HRQOL.

The existing literature on MDR-TB treatment outcomes identified several patient and clinical characteristics that might have an influence on ADRs and HRQOL. These characteristics are first defined in Chapter 2, with the possible relationship between each characteristic, ADRs, and HRQOL explored further in Chapter 3.

CHAPTER 2: Conceptual Framework

The Ferrans revision of the Wilson & Cleary HRQOL model was used to guide the development of a conceptual framework for this study (Ferrans, Zerwic, Wilbur, & Larson, 2005; Wilson & Cleary, 1995). Wilson and Cleary's original 1995 HRQOL model was unique in that it integrated the often-separate paradigms of health held by clinicians or basic science researchers and social scientists. The Wilson & Cleary framework combines the biomedical and clinical outcomes that are often of greatest interest to clinicians with the patient and well-being variables that are of interest to social scientists. Together, these variables present a more thorough portrait of a patient's HRQOL. The Wilson & Cleary model has been tested and validated in various HIV studies (Cosby, Holzemer, Henry, & Portillo, 2000; Sousa & Kwok, 2006; Vidrine, Amick, Gritz, & Arduino, 2005) and used to guide work on HIV symptoms and HRQOL in southern Africa (Holzemer, Hudson, Kirksey, Hamilton, & Bakken, 2001; Makoae et al., 2005; Phaladze et al., 2005).

After Wilson & Cleary, Ferrans and colleagues' revision of the model in 2005 is the most frequently used HRQOL model to guide research studies (Bakas et al., 2012). The Ferrans revision maintained the basic concepts of the original model, but clarified the dominant causal relationships between the concepts (Figure 1). In both the original and revised model, the uni-directional arrows did not indicate the absence of a reciprocal relationship between the concepts, instead, they were meant to demonstrate the dominant casual associations (Wilson & Cleary, 1995). Ferrans and colleagues streamlined the Wilson & Cleary model by removing the restrictions on the arrows and

removing the superfluous concept of “nonmedical factors”, which could be addressed with the remaining concepts. Due to this improved clarity of relationships between concepts, the Ferrans’ revised model was chosen over the original Wilson & Cleary model to guide this study.

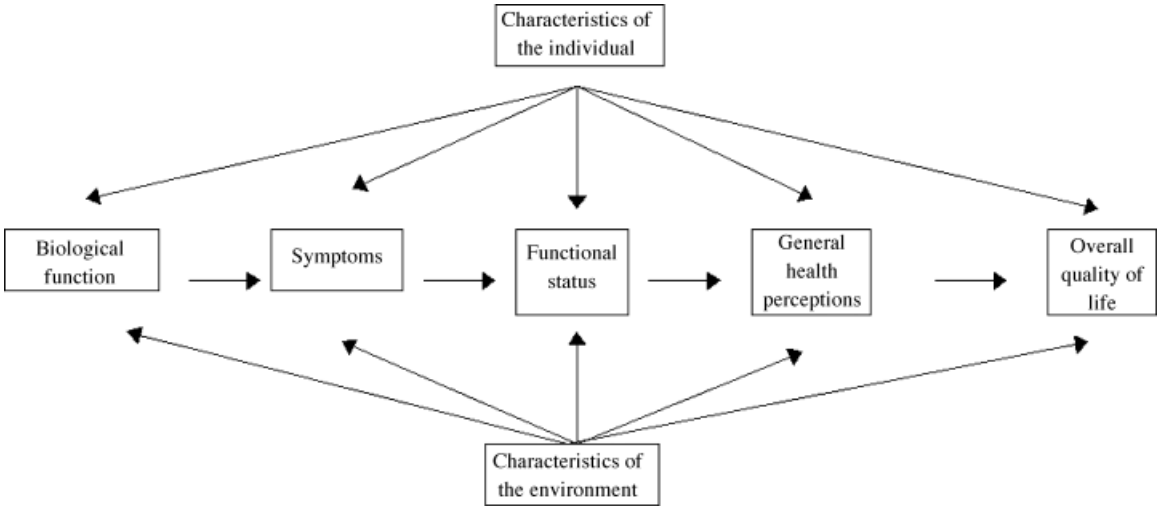


Figure 1. Ferrans et al. 2005 revision of Wilson & Cleary’s 1995 model for HRQOL. Published in “Conceptual Model of Health-Related Quality of Life”, by C. E. Ferrans, J. J. Zerwic, J. E. Wilbur, & J. L. Larson, 2005. Copyright Journal of Nursing Scholarship. Used with permission (Appendix C)

Modification to the Ferrans’ Model for MDR-TB

The Ferrans’ HRQOL model presents a linear pathway of determinants of health that ultimately influence a person’s HRQOL. It is shown in Figure 1 above without any of the modifications presented in this study. The conceptual model for this study, named the MDR-TB Treatment HRQOL model, is presented in Figure 2 below. In the Ferrans’ model, the pathway to HRQOL begins with biological function, which is measured by clinical characteristics in the MDR-TB model. In the MDR-TB model, these clinical characteristics then influence the ADRs that patients may experience

(which are identified as signs or symptoms), which in turn may affect overall HRQOL.

In Ferrans' model, there are two additional concepts of functional status and general health perception. These are important concepts related to HRQOL, but to simplify the pathway between ADRs and HRQOL in the MDR-TB model, an instrument was chosen to measure HRQOL that already encompasses functional status and health perception. The EuroQOL five dimension questionnaire (EQ-5D) includes questions on mobility, ability to perform self-care and conduct usual activities that all assess functional status. The EuroQOL visual analogue scale (EQ-VAS) is part of the EQ-5D and asks respondents to indicate their perceived health today on a scale from 0-100. This allows these important concepts of functional status and health perception to be captured in the HRQOL measure, but are not illustrated separately in the MDR-TB model.

In both Ferrans' model and the MDR-TB Treatment HRQOL model, the concepts of ADRs (or symptoms in Ferrans' model) and HRQOL may be directly affected by characteristics of the individual and or the environment. This model was chosen because it illustrated the relationship between patient characteristics (both individual and environmental), clinical characteristics and ADRs and how these ultimately impact HRQOL.

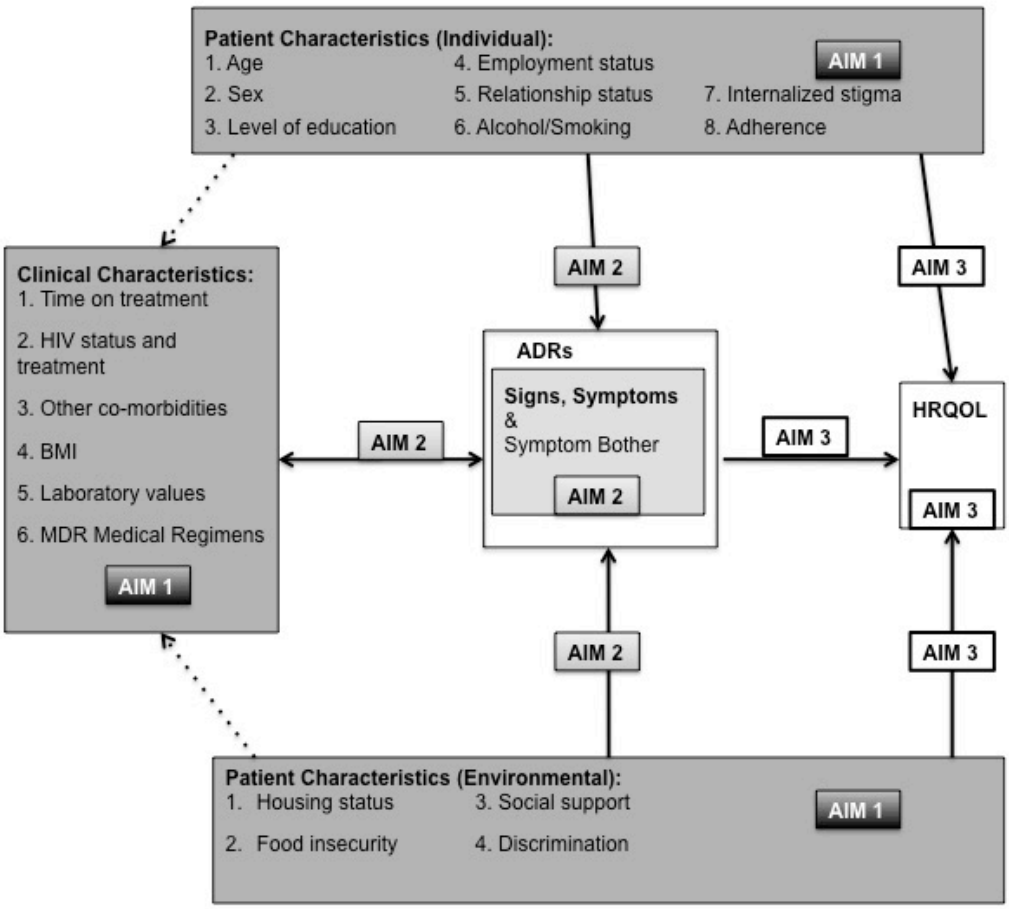


Figure 2. MDR-TB treatment HRQOL model

Patient characteristics of the individual. Although Wilson & Cleary included characteristics of the individual and the environment in their HRQOL model, they did not define the concepts in the text. The Ferrans model classified characteristics of the individual as demographic or psychological factors that influence health outcomes (Ferrans et al., 2005). The demographic variables were considered relatively unchangeable personal characteristics. For this study, these include age, sex, level of education, employment status, and relationship status. Although most of these demographic variables do have the ability to be changed, they are considered static in

comparison to psychological factors, which are dynamic, modifiable and amenable to intervention (Ferrans et al., 2005). Psychological factors include beliefs, attitudes, and behavior. Since the variables of alcohol and cigarette use and adherence relate to behavior and internalized stigma relates to belief, these three variables were considered psychological factors in this study and have been placed under the concept of characteristics of the individual. In total, this study measured eight patient characteristics of the individual. These eight variables were chosen because they were shown to have a potential effect on ADRs and/or HRQOL in previous studies, which are outlined in Chapter 3.

Conceptually, stigma is divided into "internalized stigma", also known as "perceived stigma", and "discrimination", also known as "enacted" or "external stigma" (Hasan et al., 2012). Internalized stigma is defined as the real or imagined fear of negative societal attitudes arising from an attribute considered undesirable. As a belief, it is located within the concept of characteristics of the individual. Since discrimination is a form of external stigma, it is placed under characteristics of the environment and is defined in the environmental section below.

Adherence is defined as the degree to which a patient follows the prescribed treatment schedule. Non-adherence is a significant public health problem (Morisky, Green, & Levine, 1986), especially with an airborne infectious disease such as TB. In the case of MDR-TB, continuous non-adherence can lead to treatment default. Default, recently renamed "lost to follow-up", is defined by the WHO as a patient who interrupts (drug-resistant TB) treatment for two or more consecutive months for any reason (WHO, 2014a). On average, 25% of MDR-TB patients in South Africa are lost to follow-up from

treatment (RSA DOH, 2013a).

In the MDR-TB HRQOL Treatment model, the arrows originate from the patient characteristics of the individual and influence the three concepts of clinical characteristics, ADRs, and HRQOL. Following the precedent set by the original Wilson & Cleary model, the unidirectional arrows indicate the dominant direction of these relationships. A dashed arrow has been used to indicate the relationship between individual patient characteristics and clinical characteristics because there is not a direct relationship between all the patient characteristics and all the clinical characteristics. For example, relationship status (patient characteristic) may be related to HIV status (clinical characteristic), but level of education would likely have no effect on the MDR-TB medical regimen.

Patient characteristics of the environment. According to Ferrans' model (Ferrans et al., 2005), any patient factor that is not a characteristic of the individual falls under characteristics of the environment. Specifically, these are characteristics that are either social or physical features of the patient's environment. For this study, four patient characteristics of the environment were assessed, including housing status, food insecurity, social support and discrimination. The variables of housing and food insecurity were used as indicators of socioeconomic status (SES). Food insecurity is dichotomized by severity. Low food insecurity relates to a lack of food choices, whereas very low food insecurity relates to hunger and reduced food intake (United States Department of Agriculture [USDA], 2014). This study targeted very low food insecurity.

Conceptually, discrimination, or external stigma as defined above, refers to the

negative acts of others that result from stigma (Nyblade & MacQuarrie, 2006). For this model, since discrimination refers to the acts taken by others, it has been separated from internalized stigma and is considered a patient characteristic of the environment.

Just as with the individual patient characteristics, unidirectional arrows have been used to indicate the dominant causal relationship between patient characteristics of the environment and the three concepts of clinical characteristics, ADRs, and HRQOL. A dashed arrow was used to indicate the effect of environmental patient characteristics on clinical characteristics for the same reason as the individual patient characteristics, that is, not all of the patient characteristics directly influence clinical characteristics. Aim 2 of this study focused on identifying possible relationships between the patient characteristics of the individual and the environment with ADRs.

Clinical characteristics. In the original Wilson & Cleary and Ferrans models, clinical characteristics were classified as biological variables, such as the diagnosis of disease and laboratory values (Ferrans et al., 2005; Wilson & Cleary, 1995). The reason the term clinical characteristics is used for this study is to emphasize that this study is not just looking at the effect of MDR-TB disease on HRQOL, but rather the effect of MDR-TB treatment on HRQOL. Alterations in the variables listed under clinical characteristics may directly or indirectly affect ADRs and/or HRQOL (Ferrans et al., 2005).

This study focuses on six main clinical characteristics. These six characteristics include time on MDR-TB treatment, HIV status and treatment, other co-morbidities at start of treatment, body mass index (BMI) before and during treatment, laboratory

values before and during treatment, and the MDR-TB medical regimen, including any changes to the regimen over the course of treatment.

The only bidirectional arrow in the MDR-TB model has been placed between clinical characteristics and ADRs. In the original Wilson & Cleary and Ferrans models, this arrow was unidirectional. The arrow was changed to bidirectional for this study because of the focus on MDR-TB treatment versus the effect of MDR-TB disease. The MDR-TB treatment leads to the ADRs (both signs and symptoms), but once the ADR occurs, the treating provider may choose to modify the MDR-TB medical regimen, thus leading to a back-and-forth relationship between clinical characteristics and ADRs.

In summary, clinical characteristics include both biological components of the individual, such as a diagnosed co-morbidity, and the clinical components imposed on the individual, such as the MDR-TB treatment regimen. These clinical components may be influenced by patient characteristics, both individual and environmental, and the variables listed within the concept of clinical characteristics may positively or negatively influence ADRs and/or HRQOL.

Adverse drug reactions. In the original Ferrans and colleagues (2005) and Wilson & Cleary (1995) models, the concept of ADRs was labeled “symptoms”. As noted previously, since this study is focused on the effect of treatment, the concept of symptoms has been changed to the broader term of ADRs to encompass both signs and symptoms that demonstrate an adverse reaction to treatment. In addition, symptom bother has been included to further expound on the patient’s symptom experience.

Wilson and Cleary define symptoms as a patient's perception of an abnormal physical, emotional, or cognitive state (Wilson & Cleary, 1995). This is the subjective experience of an individual (Dodd et al., 2001). Self-report is considered the gold standard for capturing an individual's symptom experience. In contrast to symptoms, signs are defined as objective measures of health change that are observable by the individual or others (Dodd et al., 2001). Wilson and Cleary note the importance of exploring other likely determinants of patient-reported symptoms, beyond only addressing the biological factors – or clinical characteristics in the MDR-TB model – as a solely biological or clinical focus is unlikely to provide full relief of the symptoms. For example, while the MDR-TB medical regimen, classified under the concept of clinical characteristics, directly influences the ADR symptoms a patient may report, the patient characteristics of the individual and the environment may also impact the symptoms reported. The MDR-TB Treatment model includes a total of 18 variables under patient and clinical characteristics that could impact the ADRs a patient experiences during MDR-TB treatment (Figure 2).

The symptom experience has been described as two dimensional: (1) the presence of the symptom and (2) the significance of the symptom to patient (Lindberg, 2006). Degree of symtom bother is one means of quantifying the patient's perception of the symptom. Symptom bother is significantly related to clinician assessment of symptom severity (Justice et al., 2001) and the patient's own assessment of symptom severity (Fairchild, Chalmers, & Begley, 2008), but is more closely linked to HRQOL than severity (Corless et al., 2005). Since HRQOL is the main variable of interest in this study, symptom bother has been chosen over symptom severity for inclusion in the

conceptual model. Symptom bother is the extent to which a patient feels they are able to tolerate a symptom, which correlates with interferece with daily activities (O'Leary, 2005). Amelioration of symptom bother has been linked to improved HRQOL (Garely, Kaufman, Sand, Smith, & Andoh, 2006). In summary, ADRs, by definition, negatively impact a patient, but the degree of impact of these signs and symptoms on HRQOL will be analyzed under Aim 3 of the study.

Health-related quality of life. The final concept in this theoretical model and the dependent outcome of this study is HRQOL. Health-related quality-of-life is an important health outcome because while physiological measures assist clinicians to revise treatment plans, these measures often correlate poorly with well-being, which is often of more interest to the patient (Guyatt et al., 1993). Furthermore, two patients with the same clinical criteria may have dramatically different responses to treatment. The original models focused on overall quality of life, which was defined as how happy or satisfied persons are with their life overall (Ferrans et al., 2005; Wilson & Cleary, 1995). This study focuses on the quality of life directly related to treatment of MDR-TB, so for that reason, HRQOL was deemed a more accurate outcome measure than overall quality of life because it focused on the well-being of the patient as influenced by the treatment (Patrick, 1997).

The conceptual framework for this study uses the concepts from the Ferrans revision to the Wilson & Cleary HRQOL model to identify possible determinants of HRQOL during MDR-TB treatment. Improved understanding of the relationship between the patient and clinical characteristics on ADRs and HRQOL will assist the clinician to tailor care during MDR-TB treatment to best improve patient's overall well-

being during a difficult medical regimen. A review of the current literature outlining the positive and negative influences of patient and clinical characteristics on ADRs and HRQOL is presented in Chapter 3.

CHAPTER 3: Review of the Literature

Health-related quality-of-life has become an important health outcome in the past few decades (Wilson & Cleary, 1995) and is of particular importance in chronic conditions. Although MDR-TB is a curable disease, the treatment duration of two years renders it more like a chronic disease. The following literature review focuses on the relationship between the variables outlined in the MDR-TB Treatment HRQOL conceptual model (Figure 2). Specifically, each patient characteristic, both individual and environmental, and each clinical variable is reviewed in relation to ADRs and HRQOL in MDR-TB populations. As there is a lack of literature on HRQOL in the drug-resistant TB population, when studies on MDR-TB populations are not available, studies conducted in drug-susceptible TB populations are used first, followed by studies in HIV populations. Health-related quality-of-life is the outcome of interest in this study and is presented first.

Health-Related Quality of Life as a Multidimensional Measure of Health

A variety of dimensions can be measured under the umbrella term of HRQOL, but most can be categorized dichotomously into physical or psychological domains (Patrick, 1997). Exploratory and confirmatory factor analyses of the various dimensions of HRQOL, including pain, fatigue, physical functioning, social activities, and mental health have supported a two-factor model for HRQOL measures, divided into physical and emotional dimensions (Hays, Bjorner, Revicki, Spritzer, & Cella, 2009).

There has been an increasing amount of research being conducted on HRQOL among drug-susceptible TB patients over the past decade after published studies called for the need for more research in this area (Aggarwal, 2010; Bauer, Leavens, &

Schwartzman, 2013; Guo et al., 2009). The findings from these studies in drug-susceptible TB populations have shown two primary outcomes: (1) treatment can improve HRQOL; (2) symptoms can persist beyond treatment and impact HRQOL.

The first finding among the review of studies related to TB and HRQOL is that HRQOL often improves during treatment, often related to reduction in TB symptoms (Bauer et al., 2013; Chamla, 2004; Guo et al., 2009; Kruijshaar et al., 2010; Maguire et al., 2009). It is unknown if this same effect would be found during MDR-TB as patients have described the treatment as "worse than the illness itself" (Isaakidis et al., 2013, p. 1130).

The second finding from the literature review is that HRQOL may be diminished for TB patients even after completing treatment, with impaired pulmonary function as the main cause (Guo et al., 2009; Maguire et al., 2009; Muniyandi et al., 2007). Both mental and physical HRQOL scores were found to be significantly lower for persons with persistent symptoms following TB treatment. MDR-TB patients also experienced a reduction in lung function after treatment completion (De Valliere & Barker, 2004). With drug-susceptible TB, the symptoms that persist beyond treatment are related to reduced lung function from the disease itself, as opposed to ADRs from the treatment. Very little has been published on the lasting effects of ADRs from MDR-TB treatment.

Although HRQOL was not measured, a graphic example of persistent symptoms from ADRs following MDR-TB treatment outcomes came from a study of five physicians in South Africa who developed MDR-TB, but were classified as cured by WHO standards. Three of the physicians were left with chronic pain and two were left with

loss of hearing, along with sporadic episodes of anxiety, short-term memory impairment and loss of bladder control (Padayatchi et al., 2010). These symptoms were all ADRs attributed to the MDR-TB treatment regimen. These lasting effects provide a clear illustration of the trade-off between increased length of life from cure and impaired quality of that life post treatment. Other MDR-TB studies have showed residual and persistent ADR effects following completion of treatment, most notably peripheral neuropathy and hearing loss and/or tinnitus (Shin et al., 2003; Sturdy et al., 2011). While depression usually resolves during treatment, anxiety has been shown to continue beyond the completion of treatment (Kruijshaar et al., 2010; Vega et al., 2004).

A study from Thailand looked at the difference in HRQOL between patients with TB, HIV, TB/HIV and MDR-TB, but with only eight MDR-TB patients (Kittikraisak et al., 2012), and found the greatest reduction in HRQOL among the MDR-TB patients. HRQOL adds to the clinical picture through the inclusion of a more comprehensive portrait of an MDR-TB patient's health status by essentially demonstrating the trade-off between the length of an individual's survival modified by how well they live (Patrick, 1997).

In a study conducted among persons with HIV, impaired ability to carry out daily activities explained the greatest variance in quality of life (Phaladze et al., 2005). Health care workers are not often aware of the degree of psychological symptoms, such as fear, distress and anxiety, that patients experience, even though these have been reported more often than physical symptoms in African HIV-positive populations (Makoae et al., 2005). As an outcome measure, HRQOL has been shown to be significantly related to clinical outcomes in patients with other forms of *Mycobacterium*

infection, such as severity of disease measured by degree of cavitary disease (Maekawa et al., 2013). Cavitary disease refers to the destruction of healthy lung tissue by the *Mycobacterium* and the replacement of lung tissue with a cavity, which can be identified by chest x-ray and is used to indicate increased severity of infection.

Impact of ADRs on HRQOL

Total number of symptoms, including ADRs from treatment, for TB patients has been significantly associated with decreased HRQOL (Chamla, 2004; Guo, Marra, Fitzgerald, Elwood, & Marra, 2010; Muniyandi et al., 2007). In HIV studies, ADRs from ART have led to significant reductions in HRQOL (Braithwaite, Goulet, Kudel, Tsevat, & Justice, 2008; Wouters, Heunis, van Rensburg, & Meulemans, 2009). Increased frequency of symptoms has shown an association with decreased HRQOL (Phaladze et al., 2005), but not always significantly so (McInerney et al., 2007; Ncama et al., 2008).

Symptom Bother. The majority of studies recording ADRs during MDR-TB treatment focus on the frequency of each ADR as recorded by the clinical provider. There is a lack of studies addressing the physiological and psychological burden of treatment-related symptoms from the patient perspective. Symptom bother provides this patient-reported measure of burden (Justice et al., 2001), by providing a means for patients to quantify how tolerable they find a symptom (O'Leary, 2005). As patients feel more bothered by symptoms arising from treatment, or unable to tolerate the symptoms, this increase in bother may lead to a decrease in adherence, as has been shown in the HIV population (Corless et al., 2005). An increase in symptom bother has also been associated with a decrease in HRQOL (Garely et al., 2006; O'Leary, 2005).

Patient Characteristics (Individual) Associated with ADRs and HRQOL

Age. The majority of MDR-TB patients are young adults in their 30s, with the average age in most MDR-TB ADR studies ranging from 26 to 49 (Ahuja et al., 2012; Wu et al., 2013). The effect of a person's age on the likelihood of developing an ADR during MDR-TB treatment varied widely among studies. An increase in age has been shown to be significantly associated with a greater risk of developing an ADR during MDR-TB treatment (Bloss et al., 2010), with some studies showing this increased risk as young as 40 (Chung-Delgado et al., 2011; Vega et al., 2004). An increase in age also increases the risk for certain ADRs, notably hearing loss from the aminoglycoside injectable (Sturdy et al., 2011). In other MDR-TB studies, there was no significant relationship found between age and ADRs (Avong et al., 2015; Carroll et al., 2012; Yew et al., 2000), while the majority of studies did not conduct an analysis for differences by age.

The relationship between age and HRQOL also varies among studies. In TB and/or HIV samples, there was not always a clear connection between HRQOL and age. Some studies found an increase in age to be a significant predictor of reduction in HRQOL (Babikako et al., 2010; Chamla, 2004; Duyan, Kurt, Aktas, Duyan, & Kulkul, 2005; Guo et al., 2008; Kittikraisak et al., 2012; Nyamathi, Berg, Jones, & Leake, 2005; Yang, Chen, Kuo, & Wang, 2003). Others found no relationship between age and HRQOL (Louw et al., 2012; McInerney et al., 2008; Nokes et al., 2011). Although findings on the effect of age during MDR-TB were not definitive, there was a persistent association between increased age and poorer health outcomes.

Sex. Few studies have looked for significant differences between males and

females in symptoms during MDR-TB treatment. Only one study demonstrated a significantly increased number of ADRs during treatment for females (Bloss et al., 2010). Carroll and colleagues found an increased odds of developing an ADR for females, but this effect was no longer significant after multivariable analysis (Carroll et al., 2012). Other MDR-TB studies found no significant differences in ADRs or overall treatment outcomes between the sexes (Malla et al., 2009; Vega et al., 2004).

For HRQOL, the majority of studies found lower HRQOL scores among females. Some studies observed that female TB patients reported poorer health outcomes, especially mental health problems, than males (Dhuria, Sharma, & Ingle, 2008; Muniyandi et al., 2007; Nyamathi et al., 2005; Yang et al., 2003). One TB study found that males had poorer HRQOL scores than females after adjusting for age (Babikako et al., 2010), while another found no significant difference in HRQOL by sex (Louw et al., 2012) There is still a gap in the literature on significant differences in ADRs and HRQOL between the sexes during MDR-TB treatment, with a trend toward worse outcomes for females.

Level of education. Studies in drug-susceptible TB and HIV populations have found both lower HRQOL (Kruijshaar et al., 2010) scores among participants with higher levels of education, and higher HRQOL with higher education (Deribew et al., 2009; Duyan et al., 2005; Louw et al., 2012), or no significant difference by educational level (Kittikraisak et al., 2012). Although there was definite variability between findings, the trend in the majority of studies was a positive correlation between higher education and improved HRQOL.

Employment status. The same positive trend was found between employment and HRQOL. Employment status is an important consideration during MDR-TB treatment. Many patients lose their jobs because they must take temporary leave from work until they have two consecutive negative sputum cultures and are no longer considered infectious. This can place great strain on a household (Aggarwal, 2010). Loss of employment has been directly linked to a decrease in HRQOL in HIV populations in South Africa (Jelsma, Maclean, Hughes, Tinise, & Darder, 2005). Neither education level or employment status was found to correlate with an increased number of adverse drug reactions among TB patients.

Relationship status. In a study to determine the incidence of psychosis during MDR-TB treatment, individuals who were unmarried were more likely to develop psychosis (Vega et al., 2004). Marriage has been shown to have a protective effect during TB treatment (Amnuaiphon et al., 2009; Guo et al., 2009). It is not clear if this positive influence would be sustained among co-habitating couples, which is the predominent relationship grouping in KwaZulu-Natal, South Africa (Hosegood, McGrath, & Moultrie, 2009).

Alcohol or cigarette use. While there was an overall association of negative TB outcomes with alcohol use, it was not always found to increase the risk of ADRs during MDR-TB treatment (Bloss et al., 2010; Shin et al., 2007). Alcohol consumption during MDR-TB treatment has been significantly associated with increased death, default and poor MDR-TB treatment outcome (Duraisamy et al., 2014; Miller et al., 2012; Shean, Willcox, & Siwendu, 2008), and less often with an increased risk of ADRs (Bezu et al., 2014). With TB treatment that includes isoniazid, alcohol consumption has been shown

to increase the risk of hepatoxicity (Døssing, Wilcke, Askgaard, & Nybo, 1996; Grant et al., 2010).

Alcohol overconsumption has a negative impact on HRQOL. TB patients classified as alcoholics documented a significantly lower score on the social dimension of HRQOL (Muniyandi et al., 2007). The same reductions in HRQOL related to alcohol use have been found in HIV populations (Braithwaite et al., 2008). The definition of alcohol abuse versus use varies by culture and country.

Cigarette use has been linked to an increased risk of initial TB infection (Barroso et al., 2003; O'Leary et al., 2014), with insufficient evidence to support a definitive effect on treatment outcomes (Slama et al., 2007). Some studies have shown a significant negative impact on TB treatment and adherence (Jain, Desai, Solanki, & Dikshit, 2014; Naidoo et al., 2013) and others have not (Abal et al., 2005). For the few MDR-TB and TB studies that analyzed the effect of cigarette use on the occurrence of ADRs, smoking was found to be an independent predictor for developing ADRs during treatment (Bezu et al., 2014; Chung-Delgado et al., 2011).

Internalized stigma. Stigma has been well documented as being highly prevalent in TB populations (Cramm, Finkenflügel, Møller, & Nieboer, 2010; Edginton et al., 2002; Long, Johansson, Diwan, & Winkvist, 2001; Macq, Solis, Martinez, Martiny, & Dujardin, 2005; Marra, Marra, Cox, Palepu, & Fitzgerald, 2004). Less has been written about the stigma associated with MDR-TB patients. Qualitative studies have documented patients' experience of both internalized stigma, feeling of shame, and experienced stigma/discrimination, social rejection and isolation (Acha et al., 2007; Sweetland,

Albújar, & Echevarria, 2002). In an MDR-TB program in Peru, one of the most significant themes in patient focus groups was profound stigma, both internal and external (Acha et al., 2007). Patients expressed feelings of guilt and shame about their disease and shared stories of rejection and discrimination from family, friends, neighbors and health providers.

Adherence. In previous studies in South Africa and other high HIV-burden populations, approximately 20-25% of the MDR-TB population defaults from treatment (Farley et al., 2011; Heller et al., 2010; Isaakidis et al., 2011). The term default, or loss-to-follow-up, is used in MDR-TB literature and refers to patients who interrupt treatment for two or more consecutive months for any reason (RSA DOH, 2013a). Low HIV-burden populations have reported lower rates of default, ranging from 10-15% (Franke et al., 2008; Tupasi et al., 2006; Van Deun, Salim, Kumar Das, Bastian, & Portaels, 2004). Inability to tolerate the adverse effects of treatment has been one of the primary causes of default (Sanchez-Padilla et al., 2014; Suárez et al., 2002; Tupasi et al., 2006; Van Deun et al., 2004), but in one South African TB study, patients with more symptoms had increased adherence (McInerney et al., 2007), which the authors' hypothesize acted as a reminder to take the medications. Other predictors or risk factors of default during MDR-TB treatment include substance use (Franke et al., 2008) and substandard housing (Franke et al., 2008). ADRs and symptom burden from ART have been found to be one of the predominant factors decreasing adherence in HIV populations (Gay et al., 2011; Nagpal, Tayal, Kumar, & Gupta, 2010; Saberi et al., 2015).

Patient Characteristics (Environmental) Associated with ADRs and HRQOL

Housing status and food insecurity. Housing status and food insecurity are

methods of measuring SES. Higher SES has been consistently correlated with improved TB treatment outcomes, adherence and HRQOL (Deribew et al., 2009; Duyan et al., 2005; Kittikraisak et al., 2012; Louw et al., 2012).

Social support. There is a clear link between perceived social support and improved HRQOL (Bekele et al., 2013; Guo et al., 2009). The link between social support and ADRs is less clear, with the greatest focus having been on the positive effect of social support on depressive symptoms during ART (Tsai et al., 2012; Yeji et al., 2014)

Discrimination. Discrimination refers to the experience of altered treatment from others, whereas internalized stigma refers to feelings a person has about his or herself in relation to a certain condition. Qualitative studies conducted in Peru found a high degree of social rejection and discrimination, with some families ostracizing MDR-TB patients, even confining them to remote parts of the house out of fear (Acha et al., 2007; Chalco et al., 2006). Often the discrimination rises from misconceptions. A community survey taken in South Africa (n=1020) found that 89% of respondents believed "only people who live in poverty get infected with TB" and "only people who are HIV positive get TB" (Cramm et al., 2010). On the reverse side, 40% believed that "all people with TB develop HIV/AIDS". Although much has been written about discrimination and stigma in HIV populations, very little has been written about discrimination in the MDR-TB population.

Clinical characteristics associated with ADRs and HRQOL

Time on treatment. Time on treatment is an important consideration for the

development of ADRs during MDR-TB treatment. Overall, ADRs are most common in the intensive phase of treatment within the first few months of treatment (Carroll et al., 2012; Isaakidis et al., 2012). Each ADR tends to manifest at different times. Gastrointestinal problems, such as nausea and vomiting, are often the first ADRs to appear (Isaakidis et al., 2012; Shin et al., 2007). Depression (Vega et al., 2004), and peripheral neuropathy (Shin et al., 2007) develop later.

The number of days on MDR-TB treatment is an important and complicated variable in the study of HRQOL. For some patients, treatment will improve their TB symptoms, such as cough, chest pain and weight loss, and this may lead to improved HRQOL. This positive effect of time on treatment was found after starting anti-TB therapy and ART in drug-susceptible TB studies and HIV studies, respectively (Guo et al., 2009; Jaquet et al., 2013; Jelsma et al., 2005; Wouters et al., 2009). For other patients, the ADRs from the treatment may be worse than the symptoms of the MDR-TB disease itself and may lead to a decreased HRQOL over time (Isaakidis et al., 2013). In HIV studies, although ART was found to increase HRQOL over time, participants with ADRs reported significantly lower HRQOL scores (Braithwaite et al., 2008; Jaquet et al., 2013; Wouters et al., 2009). It is unclear if a longer time on MDR-TB treatment will result in improved HRQOL as was shown in the HIV and drug-susceptible TB populations, or if the presence of ADRs will negate this positive effect.

HIV and ART status. HIV status has been separated from other co-morbidities, due to its high prevalence in this population. Previous studies in southern Africa have shown significantly worse MDR-TB treatment outcomes in patients co-infected with HIV without ART (Farley et al., 2011; Manda, Masenyetse, Lancaster, & van der Walt, 2013;

Seung et al., 2009). Even though the WHO guidelines (WHO, 2014a) and the South African DOH guidelines (RSA DOH, 2013a) note the increased risk for ADRs among HIV co-infected populations, this has not always been demonstrated in the literature. Most studies recording MDR-TB ADRs have been in low HIV-prevalent populations (Bloss et al., 2010; Shin et al., 2007; Törün et al., 2005), have not tested or not mentioned HIV status in the study (Carroll et al., 2012; Furin et al., 2001; Malla et al., 2009; Suárez et al., 2002; Tupasi et al., 2006; Van Deun et al., 2004) or have used HIV status as exclusion criteria (Joseph et al., 2011; Singla et al., 2009).

Multiple studies have found no significant difference in ADRs from drug-resistant TB treatment by HIV status (Avong et al., 2015; Brust et al., 2013; Mpagama et al., 2013; Shean et al., 2013; Wu et al., 2013) or did not test for significance (Sagwa et al., 2012; Seung et al., 2009). Two MDR-TB studies did find a significantly higher number of ADRs among HIV co-infected patients (Jacobs & Ross, 2012; Sagwa et al., 2014), as did drug-susceptible TB studies (Chung-Delgado et al., 2011) This variability among findings further enforces the need for additional research.

There have also been mixed findings on HRQOL among patients with TB, stratified by HIV status. Some studies have shown no significant difference by HIV status (Babikako et al., 2010), while others have found a significant negative impact of co-infection on HRQOL (Corless et al., 2009; Deribew et al., 2009; Louw et al., 2012). Persons with HIV on ART have been found to have a significantly lower quality of life than the general population (Miners et al., 2014), but among persons with HIV, ART has been shown to improve HRQOL (Jaquet et al., 2013; Jelsma et al., 2005).

Co-morbidities. Besides HIV, the three most common co-morbidities documented in the MDR-TB literature are diabetes mellitus, chronic obstructive pulmonary disease, and hypertension (Datta et al., 2009; Liu et al., 2011; Törün et al., 2005). Co-morbidities present at baseline (i.e., the start of MDR-TB treatment) have not been shown to lead to a significant increase in ADRs (Carroll et al., 2012; Liu et al., 2011; Shin et al., 2007). This may be due to the low prevalence of co-morbidities among young, and otherwise healthy, MDR-TB patients.

Body mass index (BMI). Although studies have documented poorer outcomes for underweight MDR-TB patients (Chung-Delgado, Revilla-Montag, Guillén-Bravo, & Bernabe-Ortiz, 2014; Farley et al., 2011; Joseph et al., 2011), a direct effect on ADRs has not been shown (Bloss et al., 2010; Shin et al., 2007). In one drug-susceptible TB study, weight loss during treatment was one of the greatest indicators of developing ADRs (Warmelink, ten Hacken, van der Werf, & van Altena, 2011). There is a need for further research on the effect weight changes during MDR-TB treatment might have on the development of ADRs.

Laboratory values. Standard baseline labs drawn at the start of MDR-TB treatment include K, creatinine, TSH, ALT, and Hgb. Decreased TSH is linked to Eto and para-aminosalicylic acid (PAS) and has been found to be much more common than originally believed, with the incidence of hypothyroidism during MDR-TB treatment ranging from 21%-69% (Datta et al., 2009; Modongo & Zetola, 2012; Satti et al., 2012). In drug-susceptible TB and HIV studies, anemia has been associated with an increased risk of ADRs (Chung-Delgado et al., 2011; Shivakoti et al., 2015) and a significant reduction in HRQOL (Chamla, 2004). Increased liver enzymes and rising creatinine

levels are identified in the WHO guidelines as possible risk factors for developing ADRs during MDR-TB treatment (WHO, 2014a). Overall, the literature suggests that abnormal laboratory values at the start of TB or HIV treatment may increase the risk of developing ADRs.

In summary, there is still a need for more research to determine the effect of the patient and clinical characteristics identified in the MDR-TB Treatment HRQOL model on ADRs and HRQOL in MDR-TB populations. Although the existing literature in drug-susceptible TB and HIV populations provides a useful overview of the relationships between patient and clinical characteristics, ADRs and HRQOL – namely, which characteristics positively or negatively affect ADRs and HRQOL – there is still a gap among MDR-TB populations. This study will help to fill this gap in knowledge among the MDR-TB population by measuring all of the variables outlined in this chapter using the methods presented next in Chapter 4.

CHAPTER 4: Methods

An observational, cross-sectional study design was used to determine associations between independent explanatory variables and the dependent variable of HRQOL in MDR-TB patients receiving treatment in a community-based setting in KwaZulu-Natal province, South Africa. This study utilized patient interviews, conducted by the principal investigator (PI) with a research assistant (RA) fluent in English and *isi*Zulu, to record patient characteristics, ADRs and HRQOL. Interviews were followed by medical chart data abstractions to record clinical characteristics.

Study Subjects

Inclusion criteria. The sample consisted of patients (a) 18 years of age or older receiving community-based treatment for MDR-TB (defined as receiving treatment through the outpatient clinic at the time of recruitment regardless of prior hospitalization), (b) currently in the intensive phase of treatment (the patient was still receiving the injectable aminoglycoside agent), (c) had completed at least one month (30 days) of treatment, and (d) were able to communicate in English or *isi*Zulu.

Exclusion criteria. Patients were excluded if they (a) were in the continuation phase of treatment (completed treatment with the injectable agent), (b) were initially diagnosed with XDR-TB or known to be on XDR-TB treatment, (c) presented with physical limitations that prevented them from being able to answer interview questions, or (d) presented with cognitive limitations and were unable to accurately identify the month, the president of South Africa, and why they were at the clinic the day of the interview.

Sample Size Estimate – Power Analysis

Because there was no prior information on the partial correlation between HRQOL and ADRs in the target population, the effect size of different variables on HRQOL, such as symptoms and starting ART, was extrapolated from HIV studies and ranged from 0.2 – 0.45 (Badia et al., 2000; Sherbourne et al., 2000). Partial correlation refers to the degree of association between two random variables, in this case, each ADR and HRQOL, while controlling for the effect of other random variables, in this case, the patient and clinical characteristics of the participants.

A 0.3 decrease in HRQOL was assumed as a significant decline in patient well-being for this study. To detect a partial correlation of 0.3 at 90% power, with an alpha level of 0.05 controlling for, e.g., 9 other variables, 121 patients were required. In Table 1 below, the sample sizes are presented when the number of control variables vary. Significant control variables for the data analysis were chosen from the patient and clinical characteristics in the MDR-TB Treatment model as part of the multivariable model building process outlined in the data analysis section of this chapter.

Table 1. Sample size estimates at 90% power

Number of Control Variables	Partial Correlation	Total Sample Size
3	0.2	261
3	0.3	115
6	0.2	264
6	0.3	118
9	0.2	267
9	**0.3**	**121**

Design for Sampling

A convenience sample of MDR-TB patients meeting the study criteria was obtained from the study site. Convenience sampling was chosen because it was not possible to gather data ahead of time on the patients planning to visit the clinic that day in order to institute probability sampling. The research team of the PI and RA recruited patients until the target sample size was reached.

Study Setting

King Dinuzulu Hospital (KDH) hosts South Africa's largest drug-resistant TB program, treating both MDR- and XDR-TB patients. KDH is an urban health complex with a regional general hospital, a separate 320-bed inpatient facility dedicated only to drug-resistant TB, and an outpatient clinic just beside the hospital to treat the community-based patients. Providers in the KDH drug-resistant TB clinic see over 400 patients from the community each week.

On Monday, Wednesday, and Friday, the clinic is open for new patients to be initiated on treatment. On Tuesdays and Thursdays, the clinic provides care for patients both in the intensive and continuation phases of treatment requiring monthly follow-up visits after treatment initiation. Patients already on MDR-TB treatment were approached on Tuesdays and Thursdays. KDH does not provide the daily Km injections to community-based patients. Therefore, in the intensive phase of treatment, patients receive their daily Km injections (5X/week) at another generalist clinic closer to their home or from an injection team that travels to their home. Community-based patients only return to KDH to visit with a provider once per month.

Ethical Clearance

Ethical approval was first granted by the Institutional Review Board (IRB) at Michigan State University (MSU). In South Africa, the PI received ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee and the KwaZulu-Natal DOH Research & Knowledge Management Unit. The Medical Manager and TB Clinical Manager at KDH also provided letters of support, granting the research team permission to speak to patients at the MDR-TB clinic. The PI presented an overview of the study to the KDH administration and clinic staff prior to implementation.

Risk to Human Subjects

Human subjects Involvement and characteristics. Participants in this study included individuals 18 years and older who were in the intensive phase of treatment for MDR-TB. These were patients waiting to be seen by the providers at the KDH clinic for their monthly MDR-TB appointment. One participant self-reported her age as 18, but did not have her identification card to verify her date of birth. The interview was conducted and on the following day, during the medial chart data abstraction, the participant was found to be only 17 years of age. Both the University of KwaZulu-Natal Biomedical Research Ethics Committee and the MSU IRB were notified of this deviation from the study protocol and both institutions permitted the use of the data.

Sources of materials. The PI kept identifying information in a locked room during the period of data collection. The study data was kept separately on the password-protected, web-based Research Electronic Data Capture (REDCap) data management system, with a study identification number linking the data and patient identifying information. This identifying information was used to access the patients' medical

charts from the clinic for the data abstraction. All identifiers were destroyed at the end of the data collection period.

Potential risks. Subjects were not placed in physical or financial risk by their participation in this study. There was a potential risk for subjects to incur stress related to answering questions about their health and well-being. There was a risk for loss of confidentiality of participants based on the availability of space within the clinical area.

Protection against risk. Through the consent form, participants were informed that no information would be shared that would result in their identification. Subjects were assured that all information collected would remain confidential to the maximum extent allowable by law. Participants were given the opportunity to first ask questions about the study to ensure that they understood any potential risks before consenting to their involvement in the study. To specifically protect against the risks of stress and time, participants were notified that they were allowed to stop the interview at any time without penalty. To protect confidentiality, participants were interviewed in a private area out of hearing distance from other patients and given a study identification number. In addition, participants were compensated with a voucher for 10 Rand (approximately $1 USD) of mobile phone airtime for participating in the study. At the end of the interview, patients wrote their initials on a sheet of paper to indicate that they had received the airtime, which was submitted to the grant administrator for proof of receipt and then destroyed with the identifying information.

Recruitment and informed consent. All study procedures, including recruitment and consent, were compliant with the University of KwaZulu-Natal and MSU guidelines. A consent form was written by the PI using the University of KwaZulu-Natal Biomedical

Research Ethics Committee template and revised by the MSU IRB and was read to possible participants in either English by the PI or *isi*Zulu by the RA. It was modified by the PI's dissertation committee to simplify the language for a low literacy population and then translated to *isi*Zulu and back-translated to English by a professional translation service in South Africa. Both the English and *isi*Zulu versions of the consent form were approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee.

The consent explicitly stated that the patient had the right to stop the interview at any time and that their participation was completely voluntary and refusal to participate would not influence their treatment in any way. Every participant was given a copy of the consent letter as it contained contact information for the PI, the University of KwaZulu-Natal Biomedical Research Ethics Committee and the MSU IRB. Since all data was de-identified at the end of the data collection period, it was determined that it was appropriate to use verbal consent, as opposed to a signed consent form, to not keep any record of the patients' names. The consent form has been included in Appendix B.

Recruiting Subjects

Recruitment took place from May – July 2014 after receiving ethical clearance. The PI and RA approached groups of patients waiting outside the KDH clinic and gave the same brief introduction of the study in either English or *isi*Zulu. There was not a formal script for recruitment, but each introduction was conducted in the same manner, which included the affiliation of the research team, the purpose of the study, the approximate length of the interview and the incentive for participation. It was not possible to document percentage of patients approached who were eligible for the study

as there were more than 200 patients and family members congregated around the clinic moving between audiology, phlebotomy, and pharmacy and patients were often approached more than once as they moved between the groups. In addition, many of the same patients returned to the clinic the following month and were approached again. If patients were interested, to protect patient privacy, they were pulled aside individually for a pre-enrollment screening asking: (a) if they were at least 18 years of age, (b) when they began treatment, (c) if they were still receiving injections, (d) if they were receiving XDR- or MDR-TB treatment. If they met the inclusion criteria, the rest of the recruitment process moved to a private seated area.

Data Collection

Patients were handed a copy of the consent in either English or *isi*Zulu and the RA read the form to the patient. To confirm verbal consent, the final question on the consent form stated, “is it okay to proceed with the questions and review of your medical records”, with a box for them to checkmark to indicate consent (Appendix B). Once the patient provided verbal consent, the patient was then asked for their injection card, which contained their name, their MDR-TB medical regimen, start date, medical identification number and date of birth. Once it was confirmed they met the inclusion criteria, the interview began. All patients who provided verbal consent and met the inclusion criteria completed the full interview.

Questions were then read in either English or *isi*Zulu, depending on the patient’s preference. The interview included the instruments outlined in Table 2, minus the data abstraction tool, which was used for the medical chart data abstractions. All interviews were conducted by the PI and RA together.

All data was directly entered into a laptop during the interview. The study questionnaires and data were all secured by password and firewall protection through MSU's Biomedical Research Informatics Core. The PI utilized the REDCap data management system, which allows the researcher to build their own secure data collection, storage and export database (Harris et al., 2009). REDCap provides an intuitive interface for building and managing an online database. Data integrity is ensured by field-specific validation codes for each form, such as acceptable data ranges for a specific laboratory value, radio buttons for dichotomous or categorical responses and data fields requiring all dates to be written in the DD/MM/YY format. The MSU Biomedical Research Informatics Core designed an encrypted off-line version of the REDCap questionnaire for the laptop. Data was entered off-line into the secure laptop and then uploaded once Internet access was present after leaving the clinic.

At the start of the interview, the participant was given a unique study identification number that linked their identifying information (name, date of birth, and medical identification number) to the data collected in REDCap. The identifying data was collected by the PI and RA in order to match the participant to the correct medical chart and to make sure that no patients were interviewed twice. Only the PI and RA had access to identifying data. At the end of the data collection period, the identifying data was destroyed, leaving all data on REDCap de-identified.

Quality Control and Data Management

Measures were taken to ensure the quality of the data collected for this study. First, only the PI and one RA collected data. The RA had prior experience working with MDR-TB data abstraction at another MDR-TB hospital in KwaZulu-Natal province and

was already familiar with the patient population and the medical charts. After the RA completed human subjects training, orientation began. Although all the instruments had been professionally translated into *isi*Zulu and back-translated into English, the RA read through all the instruments in *isi*Zulu and translated them back to English verbally for the PI to ensure that the questions had the same meaning in both languages. Four questions had to be slightly altered at this point, due to difference of meaning in *isi*Zulu versus English. The final selected questions have all been presented in this Methods section and Appendix A. Once the instruments were finalized, a full day of mock interviews between the PI and RA were used to practice the recruitment, enrollment, and interview procedures using the consent form and the three instruments in both languages. No remediation was needed. Interviews were not tape recorded, since the PI and RA conducted all interviews together.

The fourth instrument, the data abstraction tool, was used for the medical chart audits on the days following the interviews. The PI and RA conducted the first five medical chart reviews together to ensure consistency of data collection. After that time, the PI and RA conducted the chart audits separately, but always working in the same room in case any questions arose about how to document anything that was not covered in training. The PI reviewed all the RA's data abstractions briefly for missing data. In addition, the PI audited five charts at random to determine accuracy of RA's documentation.

Study Measures

This study was guided by the MDR-TB Treatment HRQOL model, which was designed from the Ferrans adaptation of the Wilson and Cleary HRQOL model (Ferrans

et al., 2005; Wilson & Cleary, 1995). The five concepts in the study model originally presented in Chapter 2 are *Patient Characteristics* (*Individual), Patient Characteristics (Environmental), Clinical Characteristics, ADRs,* and *HRQOL*. The four instruments utilized in this study captured variables corresponding to the five concepts of the study model. Variables are outlined in Table 2 below.

Table 2. Summary of study variables and instrumentation

Name of Instrument	MDR-TB Model Concepts	Variables	Aims of Study	Internal Reliability (α)
1.Patient Interview Questionnaire (Including MMAS-8 and revised Internalized AIDS-Related Stigma scale)	Patient Characteristics (Individual)	Age, sex, highest level of education, employment status, relationship status (and children), & alcohol/cigarette use	Aim 1	
		Internalized stigma (from revised Internalized AIDS-Related Stigma scale)	Aim 1	α=0.71 – 0.73 *(Kalichman et al., 2009; Chan et al., 2015)*
		Adherence (from MMAS-8)	Aim 1	α=0.45 – 0.61 *(Ncama et al., 2008 for 4 item; McInerney et al., 2008)*
	Patient Characteristics (Environmental)	Housing (electricity and running water), food insecurity, social support, & discrimination	Aim 1	

Table 2. (cont'd)

Name of Instrument	MDR-TB Model Concepts	Variables	Aims of Study	Internal Reliability (α)
2. Data Abstraction Tool	Clinical Characteristics	Days between MDR-TB treatment initiation and interview, hospitalization, HIV status and ART regimen including CD4 count and viral load, co-morbidities, BMI, laboratory values (K, TSH, creatinine, Hgb, and ALT), & MDR-TB medication regimen	Aim 1	
	ADRs (Signs)	Any abnormal laboratory values listed above (for K, TSH, creatinine, and ALT) since the start of treatment were recorded as ADRs	Aim 2	
3. MDR-TB Treatment Symptom Index (MT-SI) Tool	ADRs (Symptoms and Symptom Bother)	1) fatigue or loss of energy, 2) feeling dizzy or lightheaded, 3) pain, numbness or tingling in hands or feet, 4) trouble remembering or confusion, 5) nausea or vomiting, 6) diarrhea or loose bowel movements, 7) feeling sad, down or depressed, 8) feeling nervous or anxious, 9) difficulty falling or staying asleep, 10) skin problems such as rash, dryness, or itching, 11) headache, 12) loss of appetite or a change in the taste of food, 13) bloating, pain or gas in your stomach, 14) muscle aches, 15) joint pain, 16) problems with weight loss or wasting, 17) loss of hearing, 18) ringing in ear, 19) changes in vision, 20) other	Aim 2 Aim 3	α=0.91 (*Trevino et al., 2010*)
4. EQ-5D and EQ-VAS	HRQOL	EQ-5D utility score (mobility, self-care, usual activities, pain/discomfort, depression/anxiety); VAS score (perceived health today)	Aim 3	α=0.73 - 0.85 *(Dion et al., 2004; Louwagie et al., 2007)*

References: (Chan et al., 2015; Dion, Tousignant, Bourbeau, Menzies, & Schwartzman, 2004; Kalichman et al., 2009; Louwagie et al., 2007; McInerney et al., 2008; Ncama et al., 2008; Trevino et al., 2010)

Instruments

The four instruments used in this study have been included in Appendix A. More detailed explanation of how each variable was scored is presented in Appendix D and

the internal reliability for the summated scales in this study are presented in Chapter 5.

Patient interview questionnaire and data abstraction tool. The patient interview questionnaire and the data abstraction tool were designed by the PI with input from her advisory committee. The interview questionnaire contains questions to assess the eight patient characteristics of the individual (age, sex, education, employment, relationship status, alcohol/cigarette use, internalized stigma, and MDR-TB medication adherence) and four patient characteristics of the environment (housing status, food insecurity, social support and discrimination). Face validity of the patient interview questionnaire was provided by nurses working with MDR-TB patients in SA. Face validity involved the review of questions by the nursing experts to determine if the questions appeared to be valid and were likely to capture the intended concept (Nevo, 1985). The interview questionnaire was then pilot-tested among patients at KDH and another MDR-TB hospital in KwaZulu-Natal and adapted based upon both nurse and patient suggestions.

For relationship status, it was determined to combine “married, engaged or cohabitating” classifications with “boyfriend/girlfriend” based on the predominant partnership trends among the Zulu people in KwaZulu-Natal province. A large scale study conducted in the province found that by the age of 33 – the median age of participants in this study – only 18% of women and 9% of men had been married in KwaZulu-Natal (Hosegood et al., 2009). Therefore, the classification of “marriage” did not fully capture committed relationships in the sample population, nor did cohabitation, due to the high level of mobility for employment in South Africa.

The data abstraction tool was used to record clinical characteristics from the

MDR-TB medical charts. These six clinical characteristics included time on MDR-TB treatment (days since treatment initiation), HIV status (yes or no) and treatment information (antiretroviral medical regimen, CD4 count, and viral load), co-morbidities, weight at start of treatment and at time of interview, laboratory & diagnostic values (including audiology reports) at start of treatment and most current results, and MDR-TB medical regimen. The initial MDR-TB regimen was documented, along with any changes and reasons for the change to the regimen.

Stigma. Stigma was measured using four questions adapted from the Internalized AIDS-Related Stigma Scale (Kalichman et al., 2009). The four questions were modified by changing the wording from HIV to MDR-TB. This instrument has a moderately high internal consistency and test-retest reliability in a South African population (*alpha*=0.71, *r*=0.44), with similar internal consistency findings among studies in other African countries (*alpha*=0.73) (Chan et al., 2015; Tsai et al., 2013). The original scale authors suggested an abbreviated version should have limited impact on the internal consistency, with alpha dropping to 0.67 if one item was deleted. The questions included were, “it is difficult to tell people about my MDR-TB”, “I feel guilty that I have MDR-TB”, “I feel worthless because I have MDR-TB”, and “I hide my MDR-TB from others”.

The three possible responses: agree, sometimes, or disagree were collapsed into dichotomous results by combining agree and sometimes agree resulting in scores ranging from 4 (indicated the presence of stigma in all four questions) to 0 (felt no stigma). This was the same method followed by the authors of the original 6-item scale. If participants indicated that they

experienced stigma outlined in all four questions, this was classified as “high” stigma.

Discrimination. To capture discrimination, two questions were used: “Some people treated me differently after I told them I had MDR-TB” and “I have not told some people about my MDR-TB out of fear”. These two questions were used to uncover discrimination amongst HIV patients in South Africa with the Internalized AIDS-Related Stigma Scale (Kalichman et al., 2009).

Discrimination was scored as 0, 1 or 2 for each positive response indicating the presence of discrimination. The final result was dichotomized as 2 for high discrimination vs 0 or 1 for low discrimination.

Social support. Two questions were asked to assess social support: “If I were sick and needed someone to take me to the doctor, I would have someone to take me” and “I feel there is no one I can share my most private concerns and fears”. These items were selected because they were used to validate the internal stigma scale in South Africa (Kalichman et al., 2009).

Social support was scored in the same manner as discrimination, except that the second question was reverse coded and a negative response would score 1. A score of 2 also indicated high social support.

Socioeconomic status. To quantify patients’ SES, questions on housing and food insecurity were used, as income is often inconsistent in a country with such a high rate of unemployment. To assess patients’ current housing situation, they were asked if they had electricity and running water in their home. No

electricity and no running water was classified as low SES. One question was used to assess food insecurity: do you have enough food to eat every day?

Adherence. To assess adherence to the MDR-TB regimen, the eight-item Morisky Medication Adherence Survey (MMAS-8) was used. This questionnaire has been used to successfully predict adherence in an outpatient setting (Morisky, Ang, Krousel-Wood, & Ward, 2008) and was expanded from the original 4-item scale (Morisky et al., 1986). The first seven questions were as follows: “do you sometimes forget to take your medication”, “people sometimes miss taking their medicines for reasons other than forgetting; thinking over the past month, were there any days when you did not take your medicine”, “have you ever cut back or stopped your medicine without telling your doctor because you felt worse when you took it”, “when you travel or leave home, do you sometimes forget to bring along your medicine”, “did you take all your medicines yesterday”, “when you feel like your symptoms are under control, do you sometimes stop taking your medicine”, and “taking medicine every day is a real inconvenience for some people; do you ever feel hassled about sticking to your treatment plan”. The final question was: “how often do you forget or have difficulty remembering to take all your medicine”.

The questions are phrased to avoid the “yes-saying” bias since previous adherence studies have found that patients often want to give their healthcare providers positive answers. Participants respond either yes or no to the first seven questions and the final question is a 5-point Likert response. Highly adherent patients were identified with a score of 8, medium adherence with a

score of 6 to <8, and low adherence with a score of <6 (Morisky et al., 2008). This questionnaire has been used previously in KwaZulu-Natal, South Africa to examine HIV adherence and found to have an internal consistency of α = 0.61 (McInerney et al., 2008).

Laboratory values. Laboratory values were collected from the medical charts and the National Health Laboratory Service (NHLS) computer database. The normal range of values was taken from the NHLS system in South Africa. Normal K ranged from 3.5-5.1 mmol/L, TSH from 0.35-5.50 mIU/L, Hgb from 12.0-15.0 g/dL, creatinine 49-90 μmol/L, and ALT from 7-35 μ/L. Possible ADRs included hypokalemia, defined as K < 3.5 mmol/L, hypothyroidism, defined as TSH > 5.50 mIU/L, hepatic impairment, defined as ALT > 35 μ/L, and nephrotoxicity, defined as creatinine > 90 μmol/L. Anemia, defined as Hgb < 12.0 g/dL, was documented as an important clinical variable, but not as a potential ADR. The most current laboratory values at the time of the interview and the values from the start of treatment were collected. The additional signs, seizures and psychosis, were identified from medical provider documentation in the patients' medical chart.

MDR-TB Treatment Symptom Index (MT-SI) questionnaire. The original HIV Symptom Index tool was designed to guide patient-oriented research and adverse drug reaction reporting for HIV patients on a multidrug regimen (Justice et al., 2001). To test construct validity, symptom counts and symptom bother scores were found to be associated with both the physical and mental health domains of the Medical Outcomes Survey HIV HRQOL survey. The HIV Symptom Index has been used to demonstrate significant reductions in HRQOL associated with the side effects of ART (Braithwaite et

al., 2008; Jaquet et al., 2013). Other studies utilizing the HIV Symptom Index have documented a high level of internal reliability (*alpha*=0.91) (Trevino et al., 2010).

The original tool listed 20 symptoms: 1) fatigue or loss of energy, 2) fever, chills, or sweats, 3) feeling dizzy or lightheaded, 4) pain, numbness or tingling in hands or feet, 5) trouble remembering or confusion, 6) nausea or vomiting, 7) diarrhea or loose bowel movements, 8) feeling sad, down or depressed, 9) feeling nervous or anxious, 10) difficulty falling or staying asleep, 11) skin problems such as rash, dryness, or itching, 12) cough or trouble catching your breath, 13) headache, 14) loss of appetite or a change in the taste of food, 15) bloating, pain or gas in your stomach, 16) muscle aches or joint pain, 17) problems with having sex, 18) changes in the way your body looks, 19) problems with weight loss or wasting, and 20) hair loss.

Since there was no instrument to track the ADRs associated with MDR-TB treatment, the PI modified the HIV symptom index items and added three additional symptoms associated with ADRs that are unique to the MDR-TB regimen: hearing loss, tinnitus, and visual changes. Symptoms solely associated with HIV, and not MDR-TB, were removed. These included hair loss, changes in look of body, and problems having sex. The two symptoms related to TB disease were also removed to keep the focus on ADRs; these were fever and cough. The final change was the separation of muscle pain and joint pain. Nineteen symptoms remained in the tool, presented in Table 3 below, with additional space for any other symptoms the patient has noticed since the start of MDR-TB treatment. The original instrument required less than five minutes to complete and had been previously translated to *isi*Zulu. While much of the wording is the same between the original HIV symptom index and the MT-SI, the MT-SI was

translated separately into *isi*Zulu for this study by a professional translation service in South Africa.

Table 3. Common ADRs experienced during MDR-TB and HIV treatment, the language presented to participants in the MT-SI and the suspected anti-tuberculosis and ART agents

	Adverse Drug Reaction of MDR-TB treatment	**Language used in MT-SI tool or Data Abstraction Tool**	**MDR-TB Medication suspected to cause ADR τ**	**ART Medication also known to cause ADR ττ**
1	Fatigue	"Fatigue or loss of energy?"	**Eto***, H	**EFV, 3TC,** d4T
2	Dizziness	"Feeling dizzy or lightheaded?"	**Tz, Km, Mfx,** E	**EFV**
3	Peripheral neuropathy	"Pain, numbness or tingling in the hands or feet?"	**Tz**, **H**, E, Km, Eto, Mfx	**d4t,** 3TC
4	Confusion	"Trouble remembering or confusion?"	**Tz, Mfx,** E, Eto	**EFV**
5	Nausea/Vomiting	"Nausea or Vomiting?"	**Eto, PAS, Mfx, H, E, Z,** Km	**d4t, EFV, TDF, FTC, 3TC**
6	Diarrhea	"Diarrhea or loose bowel movements?"	**PAS, Mfx,** Eto, E, Km	**d4t, TDF, FTC, 3TC**
7	Depression	"Felt sad, down, or depressed?"	**Tz**, H, Mfx, Eto	**EFV, TDF**
8	Anxiety	"Felt nervous or anxious?"	**Tz,** Eto, Mfx	**EFV**
9	Insomnia	"Difficulty falling or staying asleep?"	**Tz,** Mfx, Eto	**EFV**
10	Rash/Pruritis	"Skin problems such as rash, dryness, or itching?"	**H**, Z, E, Km, Tz, Mfx, PAS	**d4t, EFV, TDF, FTC**
11	Headache	"Headache?"	**Tz, Mfx,** Km	**d4t, EFV, TDF, FTC, 3TC**
12	Anorexia	"Loss of appetite or a change in the taste of food?"	Z (anorexia), E (bitter taste of med), Eto (metallic taste)	
13	Gastritis	"Bloating, pain, or gas in your stomach?"	Eto, Z, E, PAS	3TC
14	Myalgia	"Muscle aches?"	**Z, Km** (muscle twitching) & Mfx	3TC
15	Arthralgia	"Joint pain?"	**Z**, H, E, Mfx	

Table 3. (cont'd)

	Adverse Drug Reaction of MDR-TB treatment	Language used in MT-SI tool or Data Abstraction Tool	MDR-TB Medication suspected to cause ADR τ	ART Medication also known to cause ADR ττ
16	Hearing Loss	"Loss of hearing?"	**Km**	
17	Tinnitus	"Ringing in ear?"	**Km**	
18	Optic Neuritis	"Changes in vision?"	**E**, Eto. H	
19	Hypokalemia	Abnormal decrease in potassium since start of tx	Km	
20	Hypothyroidism	Abnormal decrease in TSH since start of tx	**Eto, PAS**	
21	Hepatotoxicity	Abnormal decrease in ALT since start of tx	**H, Z**, E, Tz, Eto, Mfx, PAS	d4T, EFV, FTC
22	Nephrotoxicity	Abnormal increase in creatinine since start of tx	**Km**	**TDF**

τ References: (Nathanson et al., 2004; The Aurum Institute, 2013; WHO, 2014a, 2014b); ττ References: (The Aurum Institute, 2013; WHO, 2014b) **Bolded** medications are more strongly associated with the ADR than those not bolded; MDR-TB Medications: E=Ethambutol, Z=Pyrazinamide, H=Isoniazid, Km=Kanamycin, Eto=Ethionamide, Mfx=Moxifloxacin, Tz=Terizidone, PAS=para-aminosalicylic acid; ART Medications: EFV=Efavirenz, TDF=Tenofovir, FTC=Emtricitabine, 3TC=lamivudine, d4T=Stavudine

To further modify the HIV symptom index for MDR-TB patients, guidelines on HIV operational research by the WHO were used. Patients were first asked, "I'm going to read you a list of symptoms. Please tell me whether you have experienced any of these symptoms in the past month?" Thirty-day self-report recall of symptoms has been shown to be effective in HIV populations (Lu et al., 2008; Oyugi et al., 2004) and drug-susceptible TB populations (Kruijshaar et al., 2010). If the patient answered positively, the next question was "did the (symptom) appear before starting MDR-TB treatment?"

If the participant indicated that they had the symptom, they were then asked if the symptom was bothersome to them on a Likert scale from 1 – 4. To aid in the

understanding of the responses for symptom bother, the PI modified a technique detailed in a HRQOL study conducted among TB and HIV patients in Thailand (Kittikraisak et al., 2012). The participant was handed a visual, colorful faces scale ranging from 1) “no bother” (green smiling face), 2) “some bother” (yellow passive face), 3) “bothers me” (orange slight frown), to 4) “bothers me a lot” (red unhappy face). This tool has been included in Appendix A with the instruments. An additional open-ended question, “how have these side effects from MDR-TB treatment affected your life”, was added to the end of the tool for exploratory analysis to allow participants to expound upon the impact of ADRs on their lives.

EuroQOL five dimension (EQ-5D). The EQ-5D was designed by the EuroQOL group in 1991 to assess the multidimensional concept of HRQOL. The EQ-5D is a 5-item questionnaire plus a visual analogue scale (VAS) where the respondent marks how they feel their health is today on a scale of 0 (worst health state imaginable) to 100 (best health state imaginable). The five items on the EQ-5D include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; all items are graded as no 1) problem, 2) some problem, or 3) unable to care/extreme case. The EQ-5D has been used in South Africa for numerous HIV studies (Hughes, Jelsma, Maclean, Darder, & Tinise, 2004; Jelsma & Ferguson, 2004; Jelsma, Mkoka, & Amosun, 2008; Jelsma et al., 2005; Louwagie et al., 2007; Wouters et al., 2009). The EQ-5D was able to discriminate between subjects by disease severity, measured by viral load (Delate & Coons, 2001).

Construct validity has been determined by comparisons to the disease-specific Medical Outcomes Study HIV questionnaire. Correlations between the EQ-5D and the

HIV questionnaire ranged from 0.45 to 0.63 (Wu et al., 2002), and the EQ-5D has been shown to have similar discriminative capacity in HIV populations compared to longer HRQOL instruments such as the 15D and SF-36 (Stavem, Frøland, & Hellum, 2005). The EQ-5D has demonstrated sensitivity to change, with significant differences in HRQOL found for HIV patients reporting adverse reactions from treatment (Braithwaite et al., 2008; Wouters et al., 2009). The EQ-5D and VAS have shown acceptable test-retest reliability ranging from a reliability coefficient of 0.82 for VAS to 0.43 for the depression/anxiety dimension of the EQ-5D (Brooks, Rabin, & De Charro, 2003). The EQ-5D and VAS have been translated into over 150 languages, including *isi*Zulu. The PI registered the study with the EuroQOL group and was granted permission to use the English and *isi*Zulu versions of the instruments.

Data Analysis

Data analysis was done using Stata Statistical Software: Release 13 (StataCorp, 2013).

Aim 1. *To describe the individual and environmental patient and clinical characteristics of community-based MDR-TB patients*

Descriptive statistics for the patient characteristics (individual and environmental) and clinical characteristics identified in the MDR-TB Treatment model were calculated to present a summary of the sample of community-based MDR-TB patients. For descriptive purposes, all continuous variables were transformed into categorical variables for display, and the frequency of each category was presented as the number and percent for each variable.

All patient and clinical characteristics were then stratified by HIV status to

determine if any statistically significant differences were present in the sample. Significant differences were calculated by Pearson's chi-square test and indicated by a p-value < 0.05.

Aim 2. *To examine the relationship between Aim 1 (patient and clinical) characteristics and ADRs, including signs, symptoms, and symptom bother*

First, descriptive statistics were calculated for each of the 18 symptom ADRs collected from the MT-SI, including the degree of symptom bother for each on a scale from 1 (no bother) to 4 (bothers me a lot). The 19th symptom listed on the MT-SI, weight loss, was removed from the total ADR count since it was not an ADR, but an effect of progressive TB disease. Descriptive statistics were then calculated for the four sign (i.e., laboratory-diagnosed) ADRs that were collected from the MDR-TB medical charts.

Multiple imputations were explored to address the problem of missing data (Rubin, 1987). If less than 20% of the data were missing, mean and modal imputations were used for continuous and discrete variables, respectively. The first method employed was mean imputation, where missing values were assigned the mean of the sample for continuous variables. All laboratory measurements with less than 20% missing data were imputed in this manner. The second form of imputation was modal imputation, where missing values were assigned the mode of the sample for categorical variables.

Multivariable linear regression was then used to examine multiple explanatory variables from the list of individual and environmental patient characteristics and clinical

characteristics on the single, continuous dependent variable: total number of ADRs (Hidalgo & Goodman, 2013). The goal of the multivariable analysis was to select the independent variables, or covariates, that resulted in a best-fit model for total ADRs. In addition, the goal was to build the most parsimonious model possible, since fewer covariates decreased the standard error and increased the feasibility of use. To build a model, the stepwise process of purposeful selection outlined in Hosmer, Lemeshow, & Sturdivant was utilized (Hosmer, Lemeshow, & Sturdivant, 2013).

The first step in the purposeful selection process was to conduct a univariable linear regression. Any variable with a p-value < 0.25 was included in the model. The reason for the increased level of significance was to make sure that all important variables were included in the model in the early stage of model building.

Any covariates found to be significant at $p<0.25$ were carried into step two. In the second step, the new multivariable model was fit and the independent variables were re-assessed at the traditional level of significance, $p<0.05$. Variables that were categorical and found to be significant at one or more of their categories and non-significant in another category were tested for overall significance using the Wald test. This linear regression produced a new, smaller model for total ADRs. For step three, the regression coefficients in the new model were compared to those in the previous model. Any coefficients with a magnitude of change greater than 20% were added back in to the model. Patient and clinical characteristics were included in Table 8 if they were found to be significantly related to total ADRs.

Step four produced the preliminary main effects model. Each independent variable not selected in step one was checked for significance with the new model using the likelihood ratio test. Any variable with a p-value < 0.05 was added back into the model, as this indicated that the variable may not have been significantly related to total ADRs by itself, but that the variable was important in the presence of other covariates. Then it was possible to continue to step five and check for interactions among the independent variables in the model. Only interactions that made sense clinically were tested and only interactions that were statistically significant at $p<0.05$ were included in the final model.

Step six, the final step of the model building process, was to determine the accuracy and goodness of fit of the final model. This was done using adjusted R^2. These six steps were repeated in Aim 3 to build a HRQOL model.

Aim 3. *To examine the effect of each ADR on HRQOL, controlling for characteristics listed in Aim 1 as potential confounders*

The main aim of the study was to estimate the association between MDR-TB ADRs and HRQOL. To do so, potential confounders were assessed through univariable and multivariable analysis. Linear regressions were used with the EQ-5D HRQOL utility score as dependent variable and each of the 18 ADRs as the independent variables, controlling for patient and clinical covariates identified in Aim 1.

CHAPTER 5: Results

The primary purpose of this study was to explore the relationship between ADRs and HRQOL during MDR-TB treatment, accounting for individual, environmental, and clinical characteristics that might influence the relationship. This study addressed three aims, with HRQOL as the final dependent variable in Aim 3. The study included interviews with 121 community-based MDR-TB patients, followed by a data abstraction of their MDR-TB medical charts. This was a cross-sectional study of patients in the initial intensive phase of treatment with data retrospectively collected from the start of the MDR-TB treatment for each participant. The term "baseline" has been used to indicate any data from the start of treatment. Reliability coefficients have been calculated for the four instruments that produced composite scores: the stigma, adherence, symptom checklist and HRQOL scales.

Aim 1 Findings and Analysis

Aim 1. To describe the individual and environmental patient and clinical characteristics of community-based MDR-TB patients

The data cleaning process (including measurement, scoring, and determination of inclusion in the multivariable analysis) for each variable under the concepts of patient and clinical characteristics has been included in Appendix D. All data transformations were done in Stata 13. Operational definitions for all study measures were presented in Chapter 4 and the instruments have also been included in Appendix A. The following section presents the descriptive statistics of the study sample, divided into patient and clinical characteristics.

Sample Characteristics

Participant age ranged from 17 – 63 (*mean* = 33.1, *SD* = 8.8) and was evenly distributed between females (*n* = 62, 51.2%) and males. The majority of participants (*n* = 98, 81%) described themselves as being in a relationship at the start of treatment, and 20 participants (16.5%) ended a relationship during treatment.

Socioeconomic Status of Participants

This was a lower SES sample as evidenced by low levels of education and high levels of unemployment and hunger. The majority of participants had not continued beyond secondary school (*n* = 103, 85.1%), which is equivalent to high school in the United States. Almost a third of the sample was unemployed at the start of treatment (*n* = 37, 30.6%). Of those working, half either lost their job or had to quit (*n* = 36/72, 50%) by the time of the interview. While most participants had running water (*n* = 99, 81.8%) and electricity (*n* = 109, 90.1%) in their homes, the majority did not have enough food to eat every day. (*n* = 62, 51.2%).

HIV Co-infection Among Sample

HIV co-infection was hypothesized to be one of the most important variables affecting ADRs and HRQOL during MDR-TB treatment. The WHO uses the term co-infection in reference to the related epidemics of HIV and TB (WHO, 2014c). There was a high degree of HIV co-infection (*n* = 90, 74.4%) and of the 78 participants with a documented date of HIV diagnosis, 32 (41%) were diagnosed with HIV less than three months before starting their MDR-TB treatment. Of the 79 on ART, 31 (39.3%) started ART during their MDR-TB treatment. The most common ART regimen was a fixed-dose combination pill of EFV/TDF/FTC (57/79, 72.2%).

To determine if HIV was predictive for specific ADRs or HRQOL, it was first necessary to determine if a significant difference existed among the other variables in the study sample by HIV status. All patient and clinical characteristics were stratified by HIV status and significant differences were calculated by Pearson's chi-square test and indicated by a p-value < 0.05. For cell sizes below 5, Fisher's exact test was used. Patient characteristics are presented in Table 4.

Sample Differences by HIV Status

Both age and sex were found to have statistically significant differences by HIV status with participants older than 24 years and females more likely to be co-infected with HIV (Table 4). Participants without children were less likely to be co-infected with HIV.

Higher levels of unemployment were found among those co-infected with HIV, but change in employment status was no longer different by HIV status ($p = 0.67$). That is, HIV status did not effect whether participants lost or quit their job during MDR-TB treatment. Participants with better housing were less likely to be co-infected with HIV. This meant that the participants with the lowest SES, defined by no running water or electricity in the home, were more likely to have become infected with MDR-TB without the risk factor of HIV co-infection. This link between poverty and increased risk of TB transmission has been well documented in the literature (Farmer, 1997).

Table 4. Patient characteristics of the individual and the environment, total and by HIV status

Patient Characteristics	Total N (%) n=121	HIV infected N (%) n=90	HIV uninfected N (%) n=31	p value
Individual				
Age				<0.001***
<24	24 (19.8)	9 (10)	15 (48.4)	
25-34	45 (37.2)	39 (43.3)	6 (19.4)	
35-44	40 (33.1)	32 (35.6)	8 (25.8)	
45+	12 (9.9)	10 (11.1)	2 (6.5)	
Sex				0.014*
Female	62 (51.2)	52 (57.8)	10 (32.3)	
Male	59 (48.8)	38 (42.2)	21 (67.7)	
Education				0.344
Completed some secondary	113 (93.4)	83 (92.2)	30 (96.8)	
Beyond secondary	8 (6.6)	7 (7.8)	1 (3.2)	
Baseline Employment status				0.043*
Unemployed	37 (30.6)	32 (35.6)	5 (16.1)	
Employed or student	84 (69.4)	58 (64.4)	26 (83.9)	
Baseline Relationship status				0.557
In relationship	98 (81)	74 (82.2)	24 (77.4)	
Single	23 (19)	16 (17.8)	7 (22.6)	
Dependents				<0.001***
No children	19 (15.7)	7 (7.8)	12 (38.7)	
1+ children	102 (84.3)	83 (92.2)	19 (61.3)	
Internalized stigma†				0.417
High stigma	9 (7.4)	6 (6.7)	3 (9.7)	
Low stigma	112 (92.6)	84 (93.3)	28 (90.3)	
Adherence††				0.497
High adherence	26 (21.5)	18 (20)	8 (25.8)	
Medium or low adherence	95 (78.5)	72 (80)	23 (74.2)	
Environmental				
Housing				0.026*
No electricity or tap water in home	8 (6.6)	3 (3.3)	5 (16.1)	
Electricity & tap water in home	113 (93.4)	87 (96.7)	26 (83.9)	
Food Insecurity				0.713
Not enough food to eat everyday	62 (51.2)	47 (52.2)	15 (48.4)	
Enough food to eat everyday	59 (48.8)	43 (47.8)	16 (51.6)	
Discrimination				0.844
High discrimination	22 (18.2)	16 (17.8)	6 (19.4)	
Low discrimination	99 (81.8)	74 (82.2)	25 (80.6)	

*p<0.05, **p<0.01, ***p<0.001

† Internalized stigma presented as a dichotomous variable: high stigma (4 out of 4), low stigma (<4); †† Adherence presented as a dichotomous variable: medium to low adherence (Morisky scale score < 8), high adherence (Morisky scale score = 8).

Stigma and Discrimination

Only 9 (7.4%) participants experienced "high" stigma, defined as a positive response to all four questions in the stigma scale. Yet, from the four items, almost half of the participants agreed they felt worthless because of their MDR-TB (*n* = 53, 44.5%). Internal reliability for the internalized stigma scale was measured using Cronbach's alpha. The four items produced an α = 0.57 in this study, compared to 0.67 reported by the instrument authors for the original six-item questionnaire if one item was deleted (Kalichman et al., 2009). The original scale authors suggested an abbreviated version should have limited impact on the internal consistency, but this was not found to be the case. This may have been due to a lower sample size than the original study and revision of the scale wording from HIV to MDR-TB.

For the two questions to assess discrimination, only 22 (18%) participants answered positively to both. Due to the homogeneity of responses and the low internal reliability of the revised stigma scale, it was determined not to include stigma and discrimination in the final multivariable analyses.

Adherence

Using the MMAS-8 designations, highly adherent patients were identified with a score of 8, medium adherence with a score of 6 to <8, and low adherence with a score of <6 (Morisky et al., 2008). Even though the majority of participants fell into the 'medium adherence' category (*n* = 58, 47.9%), most of the participants classified as medium adherence scored a 7 (34/58, 58.6%), as opposed to a 6. The question that dropped their score from an 8 to a 7 was "do you feel hassled by having to take medications every day". Many respondents agreed that it was a hassle to take the

medications every day, but they still reported taking the medications. The internal consistency for the 8-item scale in this study was low at $\alpha = 0.62$. This was similar to the $\alpha = 0.61$ reported by another study conducted in a HIV-positive population in KwaZulu-Natal (McInerney et al., 2008).

Adherence was listed in the MDR-TB Treatment HRQOL model as an explanatory variable for ADRs and HRQOL. During data collection, it became evident that the ADRs were having an effect on adherence. Therefore, the direction of this relationship has been changed in the final analysis. Adherence was not included in the model building analyses in Aim 2 and 3, but instead analyzed separately as a dependent variable in Aim 2.

Table 5. Patient characteristics carried forward for analysis in Aim 2 and 3 with level of measurement identified

Patient Variable	Level of measurement at time of data collection	Level of measurement after data transformation	Classification of variable used for analysis (Reference group indicated)
Age	Continuous	Categorical	17-24 **(Ref)** 25-34 35-44 45+
Sex	Dichotomous	Dichotomous	Male **(Ref)** Female
Change in employment	Categorical	Categorical	No change **(Ref)** Lost job/school Temp leave job/school
Change in relationship	Categorical	Dichotomous	No change **(Ref)** Lost relationship
Dependents	Continuous	Dichotomous	0 **(Ref)** 1+
Housing status	Categorical	Dichotomous	Water and/or electricity **(Ref)** Neither water/electricity
Food insecurity	Dichotomous	Dichotomous	Enough to eat **(Ref)** Not enough to eat

Clinical Characteristics of Sample

Participants had been on MDR-TB treatment for a mean of 120.3 days (*SD* = 58.8, *range* = 46 – 340), or approximately four months. Although all the study participants were receiving community-based MDR-TB treatment through the clinic, 46 (38%) had been hospitalized at some point during the treatment. Co-morbidities in addition to HIV were uncommon (*n* = 29, 24%). The majority of participants started treatment at a healthy weight, with a mean BMI of 21.8.

MDR-TB Medical Regimen at KDH

At the time of the study, the standard MDR-TB regimen at KDH consisted of two first-line anti-tuberculosis medications, three second-line medications and one injectable agent (RSA DOH, 2013a), written as: Km-PZA-EMB-Mfx-Eto-Tz. Doses were weight-based. With a mean baseline weight of 58kg (*SD* = 12.9), the majority of participants in this study were prescribed the following doses (Table 6).

Table 6. Most common MDR-TB medications used in KwaZulu-Natal, South Africa

MDR-TB Medication	WHO Classification	Dosage for normal weight (51 – 70 kg)	Pill Burden & administration	Notes on inclusion in regimen
Pyrazinamide (PZA)	Group 1 – First-line oral agent	1000-2000 mg/day	2-4 500mg tablets (PO)	Standard
Ethambutol (EMB)	Group 1 – First-line oral agent	800 mg/day	2- 400mg tablets (PO)	No longer considered part of standard MDR-TB regimen, still used at time of study
Isoniazid (INH)	Group 1 – First-line oral agent	400 mg/day	1- 300mg tablet and 1- 100mg tablet	Included at KDH if patient diagnosed with MDR-TB using Xpert MTB/RIF
Kanamycin (Km)	Group 2 – Injectable agent (Aminoglycoside)	750-1000 mg/day	5 injections/week (IM)	Standard
Moxifloxacin (Mfx)	Group 3 – Fluoroquinolone (4th generation; weakly bactericidal)	400 mg/day	1- 400mg tablet (PO)	Standard
Etionamide (Eto)	Group 4 – Oral bacteriostatic second-line agent (Thioamide)	500-750 mg/day	2-3 250mg tablets nocte (PO)	Standard
Terizidone (Tz)	Group 4 – Oral bacteriostatic second-line agent	500-750 mg/day	2-3 250mg tablets nocte (PO)	Standard
Para-aminosalicylic acid (PAS)	Group 4 – Oral bacteriostatic second-line agent	8000 mg/day	1 packet of granules added to food (PO)	Substitute for Tz or Eto
Pyridoxine (B12)	Neuro-protective adjunct medication	150 mg/day	6- 25mg tablets (PO)	Standard adjunct medication

PO = by mouth, IM = intramuscular

Xpert MTB/RIF was the primary source of MDR-TB diagnosis for this patient population. Xpert MTB/RIF is a point-of-care, cartridge-based machine using polymerase chain reaction technology to amplify nucleic acid and detect both *Mycobacterium* TB and resistance to RIF in a few hours (Zeka, Tasbakan, & Cavusoglu, 2011). One major problem is that it does not detect resistance to INH. At the time of this study, all patients testing positive for RIF-resistant TB via the Xpert MTB/RIF were started on standardized MDR-TB treatment with the addition of INH. The intention was to remove the INH once the culture and drug-susceptibility testing results returned, indicating that the patient was also resistant to INH, as all results must be confirmed by culture (RSA DOH, 2013a). Yet, the final culture results were missing in a number of the charts and many patients classified as MDR-TB remained on INH indefinitely. The number of participants with missing sputum culture results was not collected as culture results was not one of the original variables proposed in the study.

The majority of participants were placed on the standardized regimen of Km-PZA-EMB-Mfx-Eto-Trd +/- INH (*n* = 99/121, 81.8%). Of the 22 who had some deviation to their starting MDR-TB regimen, the most common modification was a decreased frequency of Km from 5 doses/week to 3 doses/week (16/22, 72.7%). The main impetus for this change was hearing loss at baseline. Of the 99 on standard treatment, 44 (44.4%) were on INH. By the time of the patient interviews, 17/44 (38.6%) had been taken off INH because their sputum culture results came back resistant to INH.

Baseline Laboratory Results

The majority of participants were anemic before starting MDR-TB treatment (75/115, 65%) with a Hgb less than 12 g/dL (*mean* = 11.09, *SD* = 2.25). Of these,

42.7% (32/75) fell below 10 g/dL. Hgb level was the only variable that was significantly different by HIV status (Table 7), with those HIV infected more likely to start treatment with a low Hgb. The difference was anticipated as both the inflammatory process associated with HIV infection and ART with zidovudine are known to cause anemia (Redig & Berliner, 2013; Shivakoti et al., 2015). Although zidovudine was not part of the standard SA ART regimen, patients' previous ART regimens were not documented in the medical charts and may have included zidovudine. As females are at higher risk for anemia, a separate simple logistic regression was run to determine the effect of sex on anemia and found to be significant (OR: 8.0, 95% CI: 3.25, 19.7, $p<0.001$), but this effect was lost for more severe anemia, defined as Hgb<10 g/dL ($p = 0.509$).

For the 75% (91/121) of participants who had a documented TSH at baseline, the mean fell within the normal range at 2.52 (*SD* = 1.5), with five participants presenting with a TSH above normal. Most participants had a normal creatinine level at the start of treatment (*mean* = 61.9, *SD* = 16.1). Although the mean ALT level for participants at the start of treatment was normal (*mean* = 28.2), levels varied widely (*SD* = 24.2), and 23 participants had a slightly elevated level above 35 μ/L. The effect of starting MDR-TB treatment with an abnormal laboratory value was analyzed in Aim 2.

Table 7. Clinical characteristics, total and by HIV status

Clinical Characteristics	Total N (%)	HIV infected N (%) n=90*	HIV uninfected N (%) n=31*	p-value
Time on Treatment				0.232
≤ 4 months (120 days)	75 (62)	53 (58.9)	22 (71)	
> 4 months	46 (38)	37 (41.1)	9 (29)	
Hospitalization (at any point)				0.342
Yes	46 (38)	32 (35.6)	14 (45.2)	
No	75(62)	58 (64.4)	17 (54.8)	
Co-morbidity (not including HIV)				0.210
Present	29 (24)	19 (21.1)	10 (32.3)	
Absent	92 (76)	71 (78.9)	21 (67.7)	
Baseline BMI *(n=108)*				0.164
Underweight (<18.5)	17 (15.7)	11 (13.4)	6 (23.1)	
Normal weight (18.5-24.9)	75 (69.4)	56 (68.3)	19 (73.1)	
Overweight (≥ 25)	16 (14.8)	15 (18.3)	1 (3.8)	
Baseline Audiology				0.27
Abnormal	41 (33.9)	33 (36.7)	8 (25.8)	
Normal	80 (66.1)	57 (63.3)	23 (74.2)	
Baseline Hgb *(n=115)*				0.001**
Anemic (< 12 g/dL)	75 (65.2)	62 (73.8)	13 (41.9)	
Normal (≥12 g/dL)	40 (34.8)	22 (26.2)	18 (58.1)	
Baseline K *(n=115)*				0.068
Hypokalemia (<3.5 mmol/L)	10 (8.7)	8 (9.5)	2 (6.9)	
Normal (3.5-5.1 mmol/L)	99 (86.1)	75 (89.3)	24 (82.8)	
Hyperkalemia (>5.1 mmol/L)	4 (3.5)	1 (1.2)	3 (10.3)	
Baseline TSH *(n=91)*				0.390
Hypothyroidism (>5.50 mIU/L)	5 (5.5)	4 (6.2)	1 (3.8)	
Normal (≤5.50 mIU/L)	86 (94.5)	61 (93.8)	25 (96.2)	
Baseline creatinine *(n=114)*				0.984
Nephrotoxicity (creat >90 μmol/L)	4 (3.5)	3 (3.5)	1 (3.4)	
Normal (creat ≤90 μmol/L)	110 (96.5)	82 (96.5)	28 (96.6)	
Baseline ALT *(n=116)*				0.117
Hepatic impairment (> 35 μ/L)	23 (19.8)	20 (23.3)	3 (10)	
Normal (≤35 μ/L)	93 (80.2)	66 (76.7)	27 (90)	
Initial MDR-TB regimen				0.358
Standardized (Km-EMB-PZA-Eto-Mfx-Tz)	37 (30.6)	24 (26.7)	13 (41.9)	
Standardized + INH	62 (51.2)	50 (55.6)	12 (38.7)	
Modified regimen (Decreased frequency of Km)	16 (13.2)	12 (13.3)	4 (12.9)	
Other modifications	6 (5)	4 (4.4)	2 (6.5)	

*Total sample size (n=121) except where indicated

Multiple Imputations for Missing Data

For the patient interviews, all 121 patients were asked all the interview questions, so there was no missing data. There was considerable missing data in the medical chart abstractions. Laboratory results were often missing. Baseline laboratory results are presented here in Aim 1 and any abnormal changes in the laboratory results during the MDR-TB treatment are presented under Aim 2. All laboratory measurements with less than 20% missing data were imputed using mean imputation. This included all laboratory values at the start of treatment, besides TSH, with the number of missing values presented: Hgb (*n* = 6), K (*n* = 6), creatinine (*n* = 7), and ALT (*n* = 5). TSH had 30 missing values at baseline, which accounted for 25% of the sample size and was therefore too high to allow for imputation.

Hospitalization during treatment was the only variable for which modal imputation was used. The majority of participants were never hospitalized, so for the three missing values, they were coded as 'never hospitalized'.

In summary, 14 clinical variables were carried forward for the Aim 2 and 3 analyses and are presented in Table 8 with their level of measurement. The only variable that was significantly different by HIV status was hgb level at baseline. HIV status was considered as a possible confounder for Hgb level in Aim 2 and 3.

Table 8. Clinical characteristics carried forward for analysis in Aim 2 and 3 with level of measurement identified

Clinical Variable	Level of measurement at time of data collection	Level of measurement after data transformation for analysis	Classification of variable used for analysis (Reference group in bold)
Baseline Hgb	Continuous	Dichotomous	Anemic (< 12 g/dL) Normal (≥ 12 g/dL) **(Ref)**
Baseline K	Continuous	Dichotomous	Hypokalemia (<3.5 mmol/L) Normal (3.5-5.1 mmol/L) **(Ref)**
Baseline TSH	Continuous	Dichotomous	Hypothyroidism (>5.50 mIU/L) Normal (≤5.50 mIU/L) **(Ref)**
Baseline creatinine	Continuous	Dichotomous	Nephrotoxicity (creat >90 μmol/L) Normal (creat ≤90 μmol/L) **(Ref)**
Baseline ALT	Continuous	Dichotomous	Hepatic impairment (> 35 μ/L) Normal (≤35 μ/L) **(Ref)**
HIV status	Dichotomous	Dichotomous	HIV-positive HIV-negative **(Ref)**
Date of HIV diagnosis	Continuous	Dichotomous	≤ 3 months from start of MDR-TB treatment > 3 months before start of MDR-TB treatment **(Ref)**
ART status	Categorical	Dichotomous	On ART Not on ART **(Ref)**
Date of ART initiation	String Variable	Dichotomous	≤ 1 month from start of MDR-TB treatment > 1 month before MDR-TB treatment **(Ref)**
Time on treatment	Continuous	Dichotomous	≤ 4 months (120 days) > 4 months **(Ref)**
Hospitalization	Categorical	Dichotomous	Yes No **(Ref)**
Presence of co-morbidity	Dichotomous	Dichotomous	Co-morbidity present Co-morbidity absent **(Ref)**
Baseline BMI	Continuous	Categorical	Underweight (<18.5) Normal weight (18.5-24.9) **(Ref)** Overweight (≥ 25)
Starting MDR-TB treatment regimen	Categorical	Categorical	Standardized (Km-EMB-PZA-Eto-Mfx-Tz) **(Ref)** Standardized + INH Modified regimen (Decreased frequency of Km) Other modifications

Aim 2 Findings and Analysis

Aim 2. To examine the relationship between Aim 1 (patient and clinical) characteristics and ADRs, including signs, symptoms, and symptom bother

The individual, environmental and clinical characteristics described in Aim 1 were used as the independent, or explanatory, covariates for ADRs in Aim 2. Descriptive statistics of the ADRs are presented first, separated into symptoms with symptom bother and signs. The 18 symptom ADRs recorded during the patient interviews were then compiled into a total ADR count, which was then used as the dependent, or response, variable in the simple and multiple linear regression analyses. As discussed below, the sign or laboratory-diagnosed ADRs were not included in the total ADR count due to a high number of missing values.

Adverse drug reactions (ADRs). In the study design, ADRs were originally divided up into symptoms (subjective report from patient) and signs (objective report from laboratory results). Symptoms were assessed using the MT-SI instrument outlined in Chapter 4. Signs were recorded as abnormal changes in laboratory values from baseline, as reported under Aim 1. While both symptom ADRs and sign ADRs are presented in the descriptive analysis below, the majority of participants were missing the follow-up laboratory results necessary to determine the presence of sign ADRs. Therefore, only the 18 symptom ADRs were included in the multivariable analyses.

Symptoms. Participants were read the list of 18 symptoms from the MT-SI instrument and given the chance to report any additional symptoms. For analysis, only symptoms that were not present at the start of treatment were documented as an ADR. If the participant indicated that they had experienced

the symptom in the past 30 days, the participant was then asked if they had this symptom prior to starting treatment. If so, the symptom was not considered an adverse effect from the treatment. Only new symptoms since the start of treatment were considered ADRs. Symptoms were asked using the simplified language from the original HIV Symptom Index Tool with the actual instrument wording included in Table 9 below.

The internal consistency for the MT-SI modified symptom checklist in this study was $\alpha = 0.79$. This degree of reliability was considered acceptable, although prior reliability coefficients for the original HIV Symptom Index were reported to be as high as $\alpha = 0.91$ (Trevino et al., 2010).

Symptom Bother. A scale of 1-no bother, 2-bothers me a little, 3-bothers me, 4-bothers me a lot was used, following the structure outlined by the authors of the original HIV Symptom Index (Justice et al., 2001). Degree of bother was also used to further define an ADR, as those symptoms that did not bother participants, level 1, were removed from the total count of ADRs. The occurrence of the highest degree of bother, level 4, per ADR was presented in Table 9 below.

Table 9. Presence of symptoms as ADRs and highest degree of symptom bother as reported from the MT-SI instrument during patient interviews

ADR	Wording Used in Patient Interview from MT-SI	Presence of ADR	Percent indicating highest degree of bother (level 4) for ADR
		N (%)	N (%)
Fatigue	"Fatigue or loss of energy?"	49 (40.5%)	25 (51%)
Dizziness	"Feeling dizzy or lightheaded?"	65 (53.7%)	20 (30.8%)
Peripheral neuropathy	"Pain, numbness or tingling in the hands or feet?"	78 (64.5%)	32 (41%)
Confusion	"Trouble remembering or confusion?"	74 (61.2%)	29 (39.2%)
Nausea or vomiting	"Nausea or vomiting?"	69 (57%)	33 (47.8%)
Diarrhea	"Diarrhea or running stomach?"	31 (25.6%)	16 (51.6%)
Depression	"Felt sad, down or depressed?"	69 (57%)	31 (44.9%)
Anxiety	"Felt nervous or anxious?"	50 (41.3%)	23 (46%)
Insomnia	"Difficulty falling or staying asleep?"	83 (68.6%)	57 (68.7%)
Rash or pruritus	"Skin problems such as rash, dryness or itching?"	65 (53.7%)	35 (53.8%)
Headache	"Headache?"	34 (28.1%)	16 (47.1%)
Anorexia or change in taste of food	"Loss of appetite or a change in the taste of food?"	55 (45.5%)	29 (52.7%)
Gastritis	"Bloating, pain or gas in your stomach?"	64 (52.9%)	30 (46.9%)
Myalgia	"Muscle aches?"	61 (50.4%)	37 (60.7%)
Arthralgia	"Joint pains?"	53 (43.8%)	38 (71.7%)
Loss of hearing	"Loss of hearing?"	39 (32.2%)	19 (48.7%)
Tinnitus	"Ringing in the ear?"	48 (39.7%)	18 (37.5%)
Changes in vision	"Changes in vision?"	52 (43%)	32 (61.5%)

The MT-SI followed a standard symptom checklist structure that allowed for simple calculation of average number of ADR symptoms per patient. All but two participants experienced at least one ADR based on patient interviews, 119 (98%). In contrast, only 94 (77.7%) had at least one ADR documented in the MDR-TB medical chart. The average number of ADRs per participant reported during the interview was 8.6 symptoms (*SD* = 4.1, *range* = 0 – 18), compared to 1.4 (*SD* = 1.2, *range* = 0 – 6) documented in the medical charts. The total number of ADRs per patient recorded from the interviews has been plotted in Figure 4. The data appear to follow a normal distribution. This is supported with a skewness of -0.03, which is close to 0, equating to normal distribution. The assumption of a normal distribution is further supported by the similarity between the mean (8.6), median (9) and mode (8).

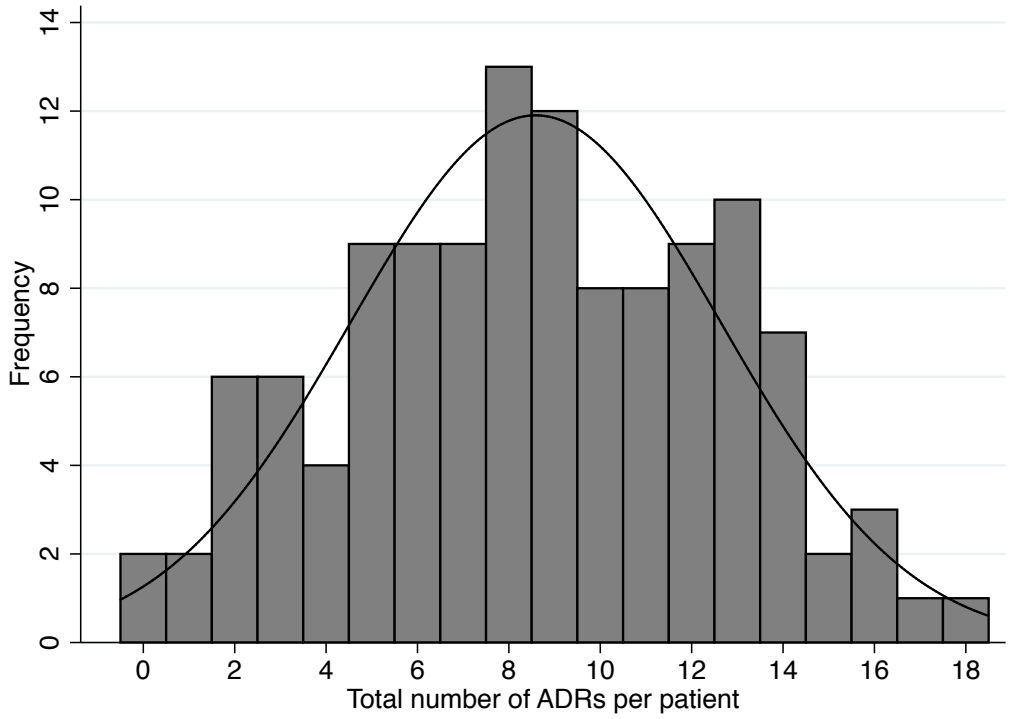


Figure 3. Histogram showing distribution of total number of ADRs reported per patient

The most common ADRs reported by the participant were insomnia 83 (68.6%), peripheral neuropathy 78 (64.5%) and confusion or trouble remembering 74 (61.2%). The most common ADRs documented in the medical charts were loss of hearing 32 (26.4%), peripheral neuropathy 22 (18.2%) and nausea/vomiting 22 (18.2%).

By percentage, the ADRs that bothered participants most (rated as a 4 on symptom bother Likert scale) were arthralgia 38/53 (71.7%), insomnia 57/83 (68.7%), changes in vision 32/52 (61.7%), and myalgia 37/61 (60.7%). The average number of most bothersome, or level 4, ADRs per participant reported during the interview was 4.2 symptoms (*SD* = 3.5, *range* = 0 – 14). No measure of bother or severity of ADRs was recorded in the medical charts.

Signs. A sign was defined as an abnormal lab value based on the South African NHLS normal values. If the baseline lab value was already abnormal, the follow-up lab result was still determined to be an ADR if the abnormal value became more severe during treatment. These values included K, TSH, creatinine, and ALT (Table 10). Hgb was not included in this analysis, as it was not directly affected by the MDR-TB medications.

Table 10. Abnormal laboratory values during MDR-TB treatment

Laboratory-diagnosed ADRs (i.e. signs)	**Number with follow-up lab results (*n=121*)**	**Number with abnormal lab results**
	N (%)	**N (%)**
Hypokalemia	83 (68.6%)	15/83 (18.1%)
Hypothyroidism	31 (25.6%)	7/31 (22.6%)
Elevated creatinine	91 (75.2%)	8/91 (8.8%)
Elevated ALT	53 (43.8%)	2/53 (3.8%)

The South African DOH MDR-TB guidelines indicate that creatinine and K should be checked every month during the intensive phase. Both Km and Eto can cause electrolyte disturbances, most notably, hypokalemia, defined as K < 3.5 mmol/L. Of the 15 participants who developed hypokalemia during treatment, eight had been placed on an oral potassium supplement. Previous studies in southern Africa have recorded a higher incidence of hypokalemia using a similar standardized MDR-TB regimen, ranging from 40%-42% (Brust et al., 2013; Seung et al., 2009). Overall, rates of abnormal lab values during treatment were found to be lower in this study than in previous studies. The reason for this is unclear.

An elevated creatinine above 90 μmol/L may indicate renal impairment. Km, the injectable aminoglycoside in the MDR-TB regimen, is potentially nephrotoxic. Of the eight participants with an elevated creatinine, seven were new cases since the start of treatment, with the eighth increasing in severity from an elevated creatinine at baseline. In three of the cases, Km was either stopped or the frequency of administration reduced. Rates of elevated creatinine were also found to be higher in previous studies, ranging from 21%-24% (Brust et al., 2013; Seung et al., 2009).

ALT is meant to be checked every 1-3 months as Km, INH and PAS all increase the chance of drug-induced hepatitis. An elevated ALT > 35 μ/L may be indicative of hepatic impairment. At the time of the interview, 53 (43.8%) participants had a follow-up ALT documented, with only two participants above 35 μ/L. Of the 21 participants who started treatment with an elevated ALT, seven (33.3%) had a normal follow-up lab result and 14 (66.7%) had no documented follow-up done. Other MDR-TB studies in sub-Saharan Africa have also reported low to no cases of hepatotoxicity (Jacobs & Ross,

2012; Mpagama et al., 2013), whereas others have found an incidence of ALT elevation as high as 49% (Brust et al., 2013).

An elevated TSH > 5.50 mIU/L may indicate hypothyroidism. Eto and PAS can inhibit thyroid hormone synthesis. Of the seven (22.6%) patients who developed hypothyroidism during treatment, four had normal TSH levels at the start of treatment and the other three did not have a baseline TSH, therefore it was not possible to determine if the elevated TSH was due to the treatment. TSH levels for these seven participants ranged from 6.32 – 25.79 mIU/L. Five of the seven (71.4%) participants with hypothyroidism were documented to be receiving levothyroxine as thyroid hormone replacement therapy. Two additional participants who had an elevated TSH at baseline were also started on levothyroxine, but had no documented follow-up TSH results. There was no documented decrease or suspension of Eto, the offending agent in the MDR-TB regimen and only one of the participants with an elevated TSH was on PAS. Overall, documented cases of hypothyroidism from treatment were not very common and were able to be managed with thyroid hormone replacement therapy without necessitating a change in the MDR-TB regimen. In a study from neighboring Lesotho, 69% of MDR-TB patients developed hypothyroidism, but 96% of those patients were receiving both PAS and Eto, which may have had an additive effect (Satti et al., 2012). Patients in this study were only receiving Eto.

In summary, less than 50% of the sample had follow-up laboratory results documented in the medical charts or in the NHLS computer system, so these values were not imputed. Therefore, laboratory ADRs were not used for the multivariable

analysis due to the high number of missing values. This included CD4 count for participants with HIV co-infection.

Management of ADRs. Many participants required a change to their MDR-TB regimen because of a known or suspected ADR (51/118, 43.2%). Eight (6.8%) patients had more than one medication stopped due to an ADR for a total of 59 medication changes due to ADRs. Once again, the most common change in the regimen (40/59, 67.8%) was the reduction in frequency or permanent discontinuation of Km injections (*n* = 35 and *n* = 5, respectively). PAS was used as the replacement medication in the five discontinuation cases. The cause of the Km reduction was due to hearing loss or tinnitus (*n* = 18), injection pain (*n* = 8), or raising creatinine levels (*n* = 3). For the remaining cases, the reason for the change was not documented.

Ethambutol was the next most commonly stopped medication, always for patient complaint of vision changes, most notably blurry vision (10/59, 16.9%). Most participants were referred to the eye clinic. Terizidone had to be stopped in three participants (5.1%) and replaced with PAS, once for seizure and twice for psychosis, which was documented as hallucinations with confusion. In three additional cases, Tz was held, reduced or split into three dosages due to dizziness. Z was stopped three times due to joint pain (5.1%) and Eto once due to abdominal pain and vomiting.

Adjunct medications were routinely given for ADRs. For nausea and/or vomiting, patients were given oral metoclopramide (*n* = 7) and for heartburn associated with gastritis they were given aluminum hydroxide and/or magnesium oxide antacids (*n* = 2). Basic analgesics were commonly prescribed along with low dose amitriptyline for

peripheral neuropathy, topical methyl salicylate anti-inflammatory rub for muscular/joint pain, and steroid cream or oral chlorphenamine anti-histamine for rash and/or pruritus.

This section concludes the descriptive analysis of the ADRs, divided into symptoms with symptom bother and signs, with related findings on treatment and management of the ADRs. In summary, ADRs during treatment were very common with almost every participant experiencing at least one ADR. The 18 ADRs identified in the MT-SI instrument have been carried forward as a single variable – total ADRs – into the principal analysis for Aim 2 along with the patient and clinical characteristics summarized in Aim 1. The data analysis section of chapter 4 describes the purposeful selection process to systematically determine which variables to include in the final effects multivariable linear regression model with total ADRs as the continuous dependent variable. Table 11 presents the final effects multivariable model with the adjusted regression coefficients.

Table 11. Univariable and multivariable linear regression analysis of patient and clinical covariates on total number of ADRs per patient

Patient and Clinical Characteristics	**Unadjusted**		**Adjusted**	
	Coef (95% CI)	***P* value**	**Coef (95% CI)**	***P* value**
Age				
17—24	1.0 (Reference)			
25—34	-0.94 (-3, 1.1)	0.363		
35—44	0.26 (-1.8, 2.3)	0.806		
45—63	-0.67 (-3.5, 2.2)	0.644		
Sex				
Male	1.0 (Reference)		1.0 (Reference)	
Female	1.71 (0.3, 3.1)	0.020*	2.48 (1, 4)	0.001**
Change in employment				
No change	1.0 (Reference)			
Lost/quit job/school	0.32 (-1.4, 2)	0.706		
Job/school temp leave	-0.36 (-1.5, 2.3)	0.710		

Table 11. (cont'd)

Patient and Clinical Characteristics	Unadjusted Coef (95% CI)	*P* value	Adjusted Coef (95% CI)	*P* value
Change in relationship status				
No change	1.0 (Reference)			
Lost relationship	-0.18 (-1.9, 1.6)	0.837		
Dependents				
0	1.0 (Reference)			
1-10	0.57 (-1.4, 2.6)	0.575		
Housing (running water & electricity)				
Yes	1.0 (Reference)			
No	-3.44 (-6.3, -0.6)	0.020*		
Food insecurity				
Enough to eat each day	1.0 (Reference)			
Not enough to eat each day	-1.15 (-2.6, 0. 3)	0.121		
Time on Treatment				
> 4 months	1.0 (Reference)			
≤ 4 months	0.56 (-0.9, 2.1)	0.462		
Hospitalization				
No	1.0 (Reference)		1.0 (Reference)	
Yes	-2.07 (-3.5, -0.6)	0.006**	-1.78 (-3.2, -0.4)	0.012*
HIV status				
Negative	1.0 (Reference)			
Positive	0.83 (-0.84, 2.5)	0.326		
Date of HIV diagnosis				
>3 months before starting MDR-TB treatment	1.0 (Reference)			
<3 months before starting MDR-TB treatment	0.52 (-1.1, 2.2)	0.537		
ART				
Yes	1.0 (Reference)			
No	-0.42 (-2, 1.1)	0.586		
Date of ART initiation				
>1 month before starting MDR-TB treatment	1.0 (Reference)			
<1 month before starting MDR-TB treatment	0.11 (-1.4, 1.6)	0.890		
Co-morbidity (besides HIV)				
Present	1.0 (Reference)			
Absent	0.18 (-1.5, 1.9)	0.835		

Table 11. (cont'd)

Patient and Clinical Characteristics	Unadjusted Coef (95% CI)	*P* value	Adjusted Coef (95% CI)	*P* value
Baseline BMI				
Normal weight (18.5-24.9)	1.0 (Reference)			
Underweight (<18.5)	0.44 (-1.7, 2.6)	0.678		
Overweight (≥ 25)	2.56 (0.4, 4.7)	0.021*		
Baseline Hgb				
Normal (≥ 12 g/dL)	1.0 (Reference)		1.0 (Reference)	
Low Hgb (< 12 g/dL)	-1.2 (-2.8, 0.3)	0.122	-2.1 (-3.7, -0.5)	0.009**
Baseline K				
Normal (3.5-5.1 mmol/L)	1.0 (Reference)			
Abnormal (<3.5 mmol/L or >5.1 mmol/L)	-0.82 (-3, 1.3)	0.453		
Baseline TSH				
Normal (≤5.50 mIU/L)	1.0 (Reference)			
Elevated TSH (>5.50 mIU/L)	-0.92 (-4.6, 2.8)	0.624		
Baseline creatinine				
Normal	1.0 (Reference)			
Elevated creatinine (creat >90 μmol/L)	2.13 (-2.1, 6.3)	0.316		
Baseline ALT				
Normal	1.0 (Reference)		1.0 (Reference)	
Elevated ALT (>35)	1.96 (0.1, 3.8)	0.036*	1.80 (0.1, 3.5)	0.040*
Baseline MDR-TB regimen				
Standardized (Km-E-Z-Eto-Mfx-Trd)	1.0 (Reference)			
Standardized + INH	0.79 (-0.9, 2.5)	0.353		
Modified regimen (Decreased frequency of Km)	0.75 (-1.7, 3.2)	0.540		
Other modifications	1.67 (-1.9, 5.2)	0.298		

CI = confidence interval, *p<0.05, **p<0.01, ***p<0.001

Effect of covariates on total ADRs. The purposeful, stepwise selection process of covariates outlined in Chapter 4 was used to build a model for total ADRs (Table 11). The final model contained two variables that were found to be significantly different by HIV status in Aim 1: sex and Hgb level at the start of treatment. Therefore, HIV status

was tested as an interaction effect, even though HIV status was not found to be significant in the unadjusted analysis. Neither interaction was significant.

The adjusted model had poor goodness of fit with an adjusted R^2 of 0.16. While each of the four explanatory covariates were all significantly associated with the total number of ADRs, they did not form a combined model with good predictive power for ADRs. Females and patients with an elevated ALT level before starting treatment experienced more total ADRs. Participants who had been previously hospitalized during their MDR-TB treatment or started treatment with a low Hgb level experienced less total ADRs. This positive effect of a low baseline Hgb level was no longer significant once the Hgb dropped to 10 g/dL. A baseline Hgb < 10 g/dL has been shown to be significantly associated with increased death during MDR-TB treatment (Seung et al., 2009). The unexpected positive effects of starting MDR-TB treatment with a low Hgb level or being hospitalized during treatment being associated with a reduced number of total ADRs are explored in Chapter 6.

Effect of ADRs on self-reported adherence. Adherence was one of the patient variables originally designated as an explanatory variable in the study's conceptual model. Using simple linear regression, the data indicate a reduction in adherence among patients who experienced a greater number of total ADRs (coeff: -0.03, 95% CI: -0.05, -0.01, p = 0.001). In addition to total ADRs, using simple logistic regression, the presence of eight specific ADRs were found to be significantly associated with a reduced odds of adherence as measured by the MMAS-8 (Table 12). High adherence (8/8 on the MMAS-8) was self-reported by 26 (21.5%) of the study participants. Since the majority of participants fell into the poor or medium adherence group (<8 on the

MMAS-8), this was used as the reference group. Therefore, the odds ratios of < 1 found for all ADRs in Table 12 demonstrate the reduced odds of having high self-reported adherence for each ADR.

Table 12. Logistic regression analysis of unadjusted effect of each ADR on self-reported adherence to MDR-TB treatment

ADR	**High adherence (MMAS 8/8)**	**Medium to low adherence (MMAS <8)**	**Effect on Reported Adherence**	***P* value**
(N)	**N (%)**	**N (%)**	**Unadj OR (95% CI)**	
Fatigue *(49)*	8 (16.3)	41 (83.7)	0.59 (0.23, 1.48)	0.257
Dizziness *(65)*	9 (13.8)	56 (86.2)	0.37 (0.15, 0.91)	0.031*
Peripheral neuropathy *(78)*	16 (20.5)	62 (79.5)	0.85 (0.35, 2.09)	0.725
Confusion *(74)*	10 (13.5)	64 (86.5)	0.30 (0.12, 0.74)	0.009**
Nausea or vomiting *(69)*	10 (14.5)	59 (85.5)	0.38 (0.16, 0.93)	0.034*
Diarrhea *(31)*	5 (16.1)	26 (83.9)	0.63 (0.22, 1.85)	0.402
Depression *(69)*	8 (11.6)	61 (88.4)	0.25 (0.10, 0.63)	0.003**
Anxiety *(50)*	4 (8)	46 (92)	0.19 (0.06, 0.60)	0.005**
Insomnia *(83)*	17 (20.5)	66 (79.5)	0.83 (0.33, 2.08)	0.691
Rash or pruritus *(65)*	12 (18.5)	53 (81.5)	0.68 (0.28, 1.62)	0.384
Headache *(34)*	3 (8.8)	31 (91.2)	0.27 (0.08, 0.97)	0.044*
Anorexia or change in taste of food *(55)*	9 (16.4)	46 (83.6)	0.56 (0.23, 1.39)	0.214
Gastritis *(64)*	8 (12.5)	56 (87.5)	0.31 (0.12, 0.78)	0.013*
Myalgia *(61)*	12 (19.7)	49 (80.3)	0.80 (0.34, 1.92)	0.624
Arthralgia *(53)*	10 (18.9)	43 (81.1)	0.76 (0.31, 1.84)	0.536
Loss of hearing *(39)*	7 (17.9)	32 (82.1)	0.73 (0.28, 1.90)	0.514
Tinnitus *(48)*	10 (20.8)	38 (79.2)	0.94 (0.38, 2.28)	0.887
Changes in vision *(52)*	5 (9.6)	47 (90.4)	0.24 (0.08, 0.70)	0.009**

Unadj OR = unadjusted odds ratio; CI = confidence interval; *p<0.05, **p<0.01, ***p<0.001

The three neuropsychiatric ADRs – anxiety, depression, and confusion – were most significantly associated with a reduction in self-reported adherence, in addition to vision changes. The related GI ADRs of nausea/vomiting and gastritis and the related ADRs of headache and dizziness were also all significantly associated with a reduction in adherence. Adherence was moved in the MDR-TB Treatment HRQOL model from individual characteristics to clinical characteristics and explained further in Chapter 6.

Additional Findings

Although not originally included in the specific aims of the study, a lack of concordance was discovered between ADRs documented in the medical charts and ADRs reported by patient interview. This is presented in Figure 4. In light of the significant relationship between anxiety, depression, and reduced adherence, of particular interest is the lack of recording of depression and anxiety in the medical charts. That is, by providers failing to recognize the presence of anxiety and depression among patients, they may be missing a clinical variable that could help them identify patients with an increased odds of non-adherence.

Percent agreement, the kappa statistic, and McNemar's test were used to determine the degree of concordance between the ADRs reported by the patient and the ADRs documented in the medical record. Kappa scores ranged from -0.007 (poor) to 0.23 (fair); percent agreement ranged from 33% to 75%. All ADRs were found to be significantly different by data source using McNemar's test ($p < 0.001$), except for hearing loss ($p = 0.26$), which had the highest kappa score ($kappa = 0.23$), likely due to the baseline and monthly audiology screenings to address the high degree of ototoxicity related to aminoglycoside administration. This probable underreporting of ADRs by

providers has important implications for clinical practice and policy development and has been addressed further in Chapter 6.

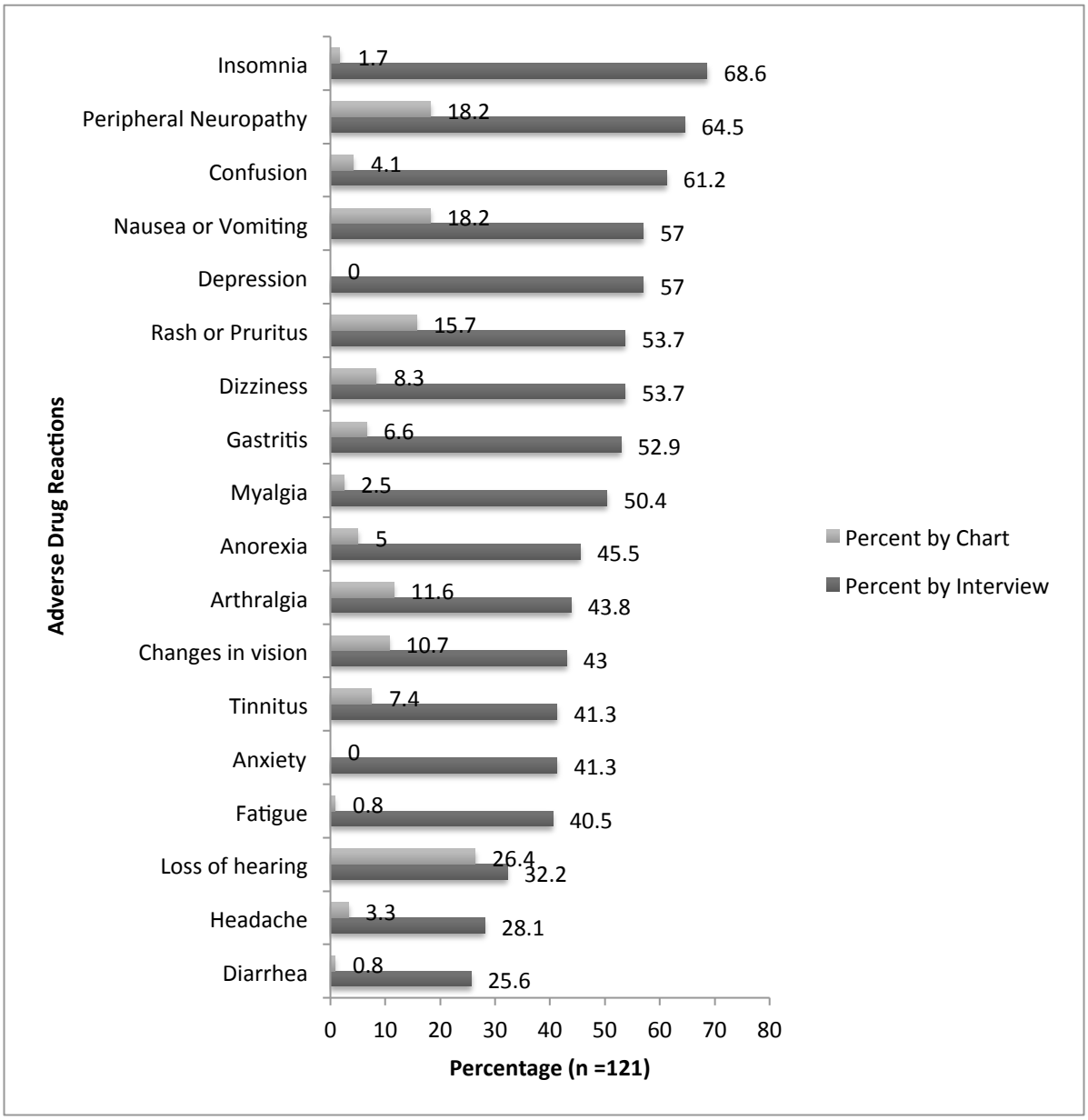


Figure 4. Percentage of ADRs reported during the participant interviews compared to the percentage of ADRs recorded in the medical charts.

Summary of Aim 2

From the results of the descriptive analysis of symptoms in Aim 2, there was a very high frequency of ADRs, which were very bothersome to participants. Although most of the findings from this study support previously published ADR findings in southern Africa, higher frequencies for specific ADRs were found in this study, notably insomnia and vision changes, and have been addressed in Chapter 6. The main purpose of Aim 2 was to explore the effect of patient and clinical covariates on total ADRs. While the effect of female sex and elevated baseline ALT levels on increased total ADRs made clinical sense, the relationship between prior hospitalization and decreased Hgb levels on decreased total ADRs was not expected and these relationships have been interpreted in Chapter 6.

Aim 3 Data Analysis

Aim 3. To examine the effect of each ADR on HRQOL, controlling for characteristics listed in Aim 1 as potential confounders

This final aim of this study combined the variables analyzed in Aim 1 and 2 as covariates on the dependent outcome of HRQOL to answer the main research question of the study: which ADRs most negatively impact MDR-TB patients? Descriptive analysis and measurement of HRQOL findings from the EQ-5D and EQ-VAS instruments have been presented first. Using the EQ-5D HRQOL utility score as the dependent variable, the ADRs from Aim 2 were used as explanatory covariates to determine which ADRs had the greatest effect on HRQOL. The final analysis added the variables from Aim 1 into the regression model as covariates to determine if and how they influence the relationship between ADRs and HRQOL.

Descriptive analysis of HRQOL. Data from the EQ-5D was analyzed in two formats as outlined by the EuroQOL group who designed the instrument. First, data have been presented as a frequency of each of the five domains in the instrument (Table 13). The three EQ-5D response levels have been dichotomized into no problems (level 1) and problems (level 2 and 3). This method was recommended by the EuroQOL group when reported numbers of level 3 problems are very low. The five dimensions were also tested for the possibility of differences by HIV status, using chi-square, but no significant differences were found.

Table 13. HRQOL of study participants, total and by HIV status

HRQOL EQ-5D dimensions	**Total N (%)** (n=121)	**HIV Infected N (%)** (n=90)	**HIV Uninfected N (%)** (n=31)	***P* value**
Mobility				0.653
No problems	70 (57.9)	51 (56.7)	19 (61.3)	
Problems	51 (42.1)	39 (43.3)	12 (38.7)	
Self-Care				0.955
No problems	98 (81)	73 (81.1)	25 (80.7)	
Problems	23 (19)	17 (18.9)	6 (19.4)	
Usual Activities				0.329
No problems	52 (43)	41 (45.6)	11 (35.5)	
Problems	69 (57)	49 (54.4)	20 (64.5)	
Pain/Discomfort				0.384
No problems	51 (42.1)	40 (44.4)	11 (35.5)	
Problems	70 (57.9)	50 (55.6)	20 (64.5)	
Anxiety/Depression				0.936
No problems	71 (58.7)	53 (58.9)	18 (58.1)	
Problems	50 (41.3)	37 (41.1)	13 (41.9)	

Of the five dimensions in the EQ-5D, participants had the most problems with pain. Many of the ADRs associated with treatment are painful: peripheral neuropathy, headache, gastritis (abdominal pain), myalgia and arthralgia. In addition, numerous participants mentioned the pain of the intramuscular Km injections. The majority of

participants also had problems performing their usual activities (such as work, study, study, housework, family or leisure activities).

One potential limitation with the EQ-5D is the high likelihood of ceiling effect, when a large number of participants select the highest response score. In this study, a small percentage of participants (*n* = 17, 14%) indicated no problems in all five categories, compared to a large population-based study that found a 33% ceiling effect from respondents with at least one medical condition (Franks, Hanmer, & Fryback, 2006). Nevertheless, the results from the summary score were still negatively skewed at -0.90 (Figure 5). In a left-skewed distribution, the mode > median > mean, which was the case with the HRQOL utility score, mode = 1.0, median = 0.79, and mean = 0.74.

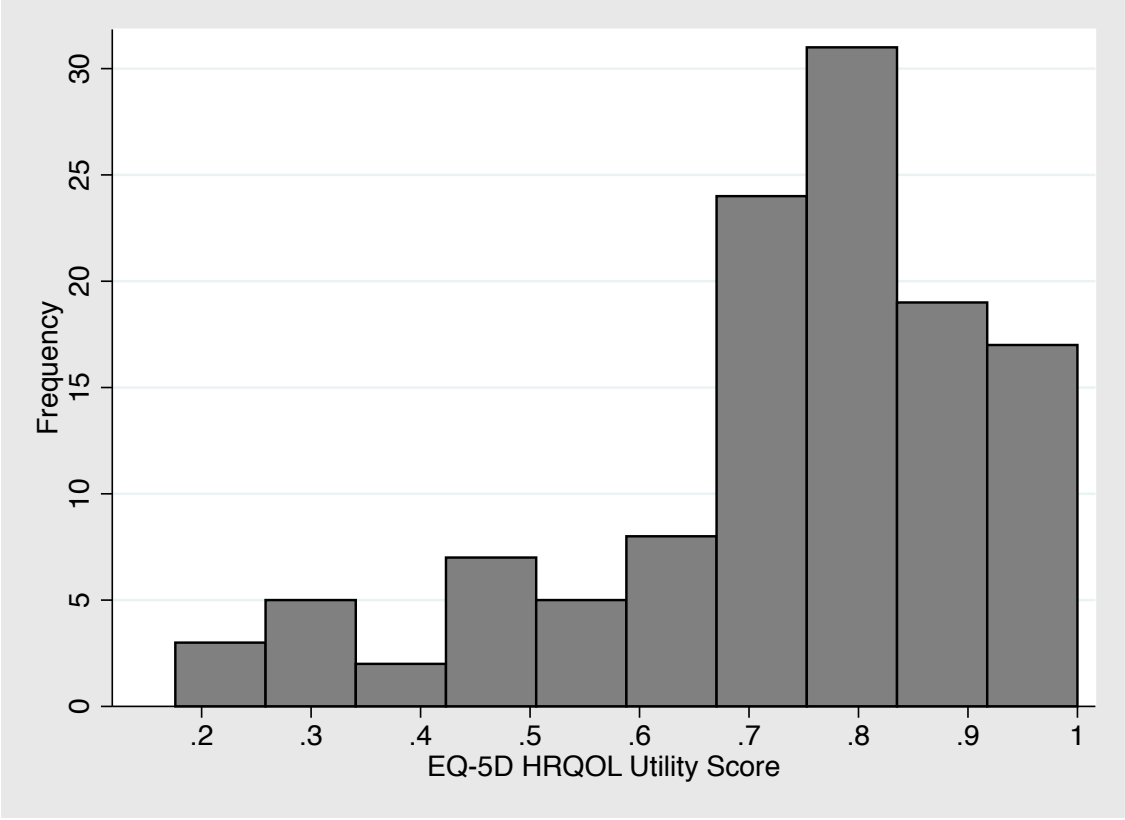


Figure 5. Histogram showing distribution of EQ-5D HRQOL utility score

Figure 5 presents the results from the second method for presenting the data from the EQ-5D, which is to transform each patient response into a utility score using weights from a representative value set. This results in a single summary index score for all participants, which can mathematically range from -0.15 to 1.0, with greater scores indicating better overall health (Revicki et al., 2009).

The representative weights for each health state were taken from the only value set conducted in sub-Saharan Africa, specifically, in the neighboring country of Zimbabwe (Jelsma, Hansen, De Weerdt, De Cock, & Kind, 2003). This Zimbabwean valuation study used the time trade-off method to determine quality of life weights, in which respondents chose the length of time they were willing to live in a specific health state below optimal health. The model produced from the valuation study ranked the optimal health state as 1.0 (health status: 11111) and the worst health state (33333) as -0.145. For this study, the EQ-5D utility score was used as the sole outcome variable for the multivariable analysis in Aim 3. The mean utility score for this sample was 0.74 (*SD* = 0.19, *range* = 0.18 – 1.0), which fell within the anticipated range of 0.7 – 0.75 for people suffering from mental and physical health illness. Scores less than 0.5 are rarely seen, with scores from large population studies finding that respondents with chronic disease that affects both their mental and physical health score between 0.7 – 0.75, on average (Miners et al., 2014; Revicki et al., 2009).

Cronbach α for the EQ-5D in this study was low at 0.64. A similar study in South Africa to determine HRQOL during ART for persons with HIV found an alpha of 0.85 using the EQ-5D (Louwagie et al., 2007). It is unclear what might have led to the lower

internal reliability within the EQ-5D found in this study, although some sources classify any alpha > 0.60 as good (Nunnally, 1967).

The EuroQOL Visual Analogue Scale (EQ-VAS) is a separate, sixth question from the EQ-5D, which asks participants to define their current health on a scale from 0 (worst imaginable health) – 100 (best imaginable health). Although the brief instructions were read verbatim in English or *isi*Zulu to the participant during the interview, some participants seemed to struggle to understand the scale. This potential misinterpretation was difficult to quantify as participants did not explain why they chose a certain number on the scale. The mean EQ-VAS score was 67.8 (*SD* = 22.4, *range* = 0-100). The correlation between the EQ-5D utility score and the EQ-VAS was 0.45, which is generally considered a moderate strength of relationship between the scores. This challenge to the validity of the VAS has been documented previously (Feng, Parkin, & Devlin, 2014). Due to this challenge, the EQ-5D utility score was chosen over the VAS score as the final outcome measure.

Effect of ADRs on HRQOL. Following the same six-step model-building procedure outlined in Chapter 4, a univariable and multivariable analysis of HRQOL was conducted. The utility score was used as the outcome variable and the ADRs were used as the explanatory covariates (Table 14). Due to the large number of covariates that were tested, they were divided into two analyses presented in Table 14 and 15. Table 14 tests for significance between each ADR and each ADR at the highest level of bother on HRQOL. Total ADRs and total most bothersome ADRs are included in the univariable analysis, but have not been included in the multivariable analysis due to potential collinearity with the specific ADRs.

Table 14. Univariable and multivariable linear regression analysis for ADR effect on HRQOL

ADRs	Unadjusted		Adjusted	
	Coefficient (95% CI)	***P* value**	**Coefficient (95% CI)**	***P* value**
Fatigue	-0.06 (-0.1, 0.01)	0.106		
Bothersome fatigue	-0.12 (-0.2, -0.04)	0.005**		
Dizziness	-0.07 (-0.1, -0.06)	0.034*		
Bothersome dizziness	-0.15 (-0.2, -0.06)	0.001**		
Peripheral neuropathy	-0.13 (-0.2, -0.06)	<0.001***		
Bothersome peripheral neuropathy	-0.17 (-0.2, -0.09)	<0.001***	-0.09 (-0.15, -0.03)	0.006**
Confusion	-0.08 (-0.2, -0.01)	0.024*		
Bothersome confusion	-0.07 (-0.15, 0.01)	0.084		
Nausea/Vomiting	-0.15 (-0.2, -0.08)	<0.001***	-0.10 (-0.16, -0.05)	<0.001***
Bothersome Nausea/Vomting	-0.15 (-0.23, -0.08)	<0.001***		
Diarrhea	-0.11 (-0.18, -0.03)	0.007**		
Bothersome diarrhea	-0.22 (-0.31, -0.13)	<0.001***	-0.15 (-0.23, -0.07)	<0.001***
Depression	-0.09 (-0.16, -0.03)	0.007**		
Bothersome depression	-0.09 (-0.17, -0.02)	0.018*		
Anxiety	-0.09 (-0.16, -0.02)	0.009**		
Bothersome anxiety	-0.17 (-0.25, -0.08)	<0.001***		
Insomnia	-0.08 (-0.15, -0.01)	0.029*		
Bothersome insomnia	-0.05 (-0.12, 0.02)	0.175		
Rash	-0.09 (-0.16, -0.02)	0.008**		
Bothersome rash	-0.06 (-0.13, 0.02)	0.137		
Headache	-0.08 (-0.15, -0.00)	0.049*		
Bothersome headache	-0.07 (-0.17, 0.03)	0.160		

Table 14. (cont'd)

ADRs	Unadjusted Coefficient (95% CI)	*P* value	Adjusted Coefficient (95% CI)	*P* value
Anorexia	-0.09 (-0.16, -0.03)	0.007**		
Bothersome anorexia	-0.17 (-0.24, -0.09)	<0.001***		
Gastritis	-0.08 (-0.15, -0.01)	0.026*		
Bothersome gastritis	-0.07 (-0.15, 0.01)	0.086		
Myalgia	-0.17 (-0.23, -0.11)	<0.001***	-0.07 (-0.13, -0.01)	0.032*
Bothersome myalgia	-0.15 (-0.22, -0.08)	<0.001***		
Arthralgia	-0.17 (-0.24, -0.11)	<0.001***	-0.07 (-0.13, -0.01)	0.030*
Bothersome arthralgia	-0.17 (-0.24, -0.11)	<0.001***		
Hearing loss	-0.10 (-0.17, -0.02)	0.010*		
Bothersome hearing loss	-0.07 (-0.17, -0.02)	0.141		
Tinnitus	-0.08 (-0.15, -0.01)	0.019*	-0.06 (-0.11, -0.01)	0.028*
Bothersome tinnitus	-0.10 (-0.19, -0.00)	0.047*		
Vision changes	-0.09 (-0.16, -0.03)	0.007**		
Bothersome vision changes	-0.12 (-0.19, -0.04)	0.003**		
Total ADRs	**-0.03 (-0.03, -0.02)**	**<0.001*** **		
Total Most Bothersome ADRs	**-0.03 (-0.04, -0.02)**	**<0.001*** **		

*p<0.05, **p<0.01, ***p<0.001

As hypothesized, an increase in the number of total ADRs was significantly related to a decrease in HRQOL. The regression line for the unadjusted analysis was y = 0.96 – 0.03x (Figure 5) with a goodness of fit of R^2 = 0.31. Figure 5 also represents the linear relationship between total number of ADRs and HRQOL.

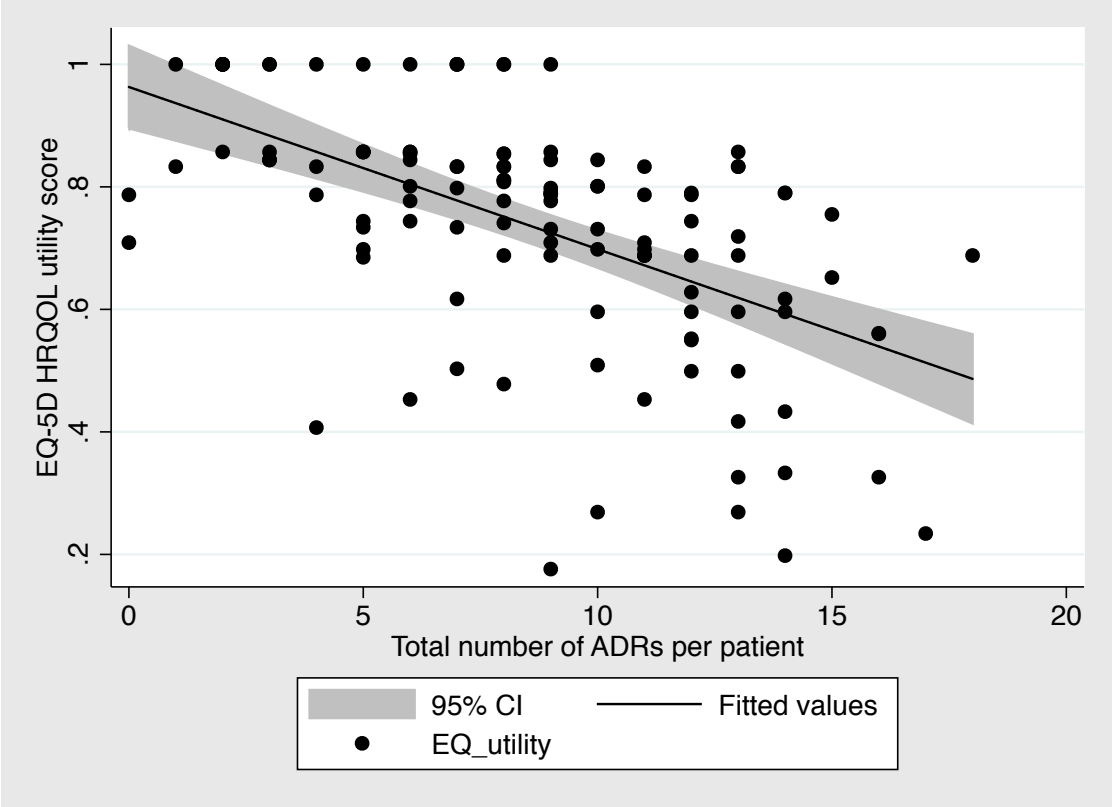


Figure 6. Scatterplot and univariable linear regression with 95% confidence interval for EQ-5D HRQOL utility score as a function of the total number of ADRs reported per patient

While it was predicted that ADRs would negatively impact HRQOL, the main question in Aim 3 was to determine which ADRs were significantly associated with a decrease in HRQOL. The results from the multivariable analysis indicated that four ADRs had the most significant, negative impact on the participants' HRQOL, regardless of the degree of bother. These included: nausea/vomiting, myalgia, arthralgia, and tinnitus. When only the most bothersome ADRs were analyzed (i.e. ADRs designated the highest level of bother with a score of 4), the two ADRs that remained significant were diarrhea and peripheral neuropathy.

Effect of patient and clinical characteristics on HRQOL. A simple linear regression analysis was conducted with each Aim 1 patient and clinical characteristic as the explanatory covariate and the HRQOL utility score as the dependent variable (Table 15). Following the purposeful selection process, all variables with a p-value<0.25 were carried forward for the multivariable analysis. Only variables significant at the traditional p<0.05 level are presented in the adjusted analysis.

Table 15. Univariable and multivariable linear regression analysis of patient and clinical covariates on HRQOL

Patient and Clinical Characteristics	**Unadjusted**		**Adjusted**	
	Coef (95% CI)	***P* value**	**Coef (95% CI)**	***P* value**
Age				
17—24	1.0 (Reference)			
25—34	0.04 (-0.05, 0.14)	0.382		
35—44	0.02 (-0.08, 0.12)	0.690		
45—63	-0.02 (-0.16, 0.11)	0.735		
Sex				
Male	1.0 (Reference)			
Female	-0.02 (-0.09, 0.05)	0.555		
Change in employment				
No change	1.0 (Reference)			
Lost/quit job/school	0.03 (-0.05, 0.11)	0.461		
Job/school temp leave	-0.02 (-0.12, 0.07)	0.719		
Change in relationship status				
No change	1.0 (Reference)		1.0 (Reference)	
Lost relationship	-0.06 (-0.15, 0.02)	0.130	-0.08 (-0.16, 0.002)	0.044*
Dependents				
0	1.0 (Reference)			
1-10	0.04 (-0.06, 0.13)	0.409		
Housing (running water & electricity)				
Yes	1.0 (Reference)			
No	0.05 (-0.09, 0.19)	0.449		
Food insecurity				
Enough to eat each day	1.0 (Reference)			
Not enough to eat each day	0.03 (-0.04, 0.10)	0.369		

Table 15. (cont'd)

Patient and Clinical Characteristics	Unadjusted Coef (95% CI)	*P* value	Adjusted Coef (95% CI)	*P* value
Time on Treatment				
> 4 months	1.0 (Reference)			
≤ 4 months	-0.06 (-0.13, 0.01)	0.075		
Hospitalization				
No	1.0 (Reference)		1.0 (Reference)	
Yes	0.12 (0.06, 0.19)	<0.001***	0.13 (0.07, 0.2)	<0.001***
HIV status				
Negative	1.0 (Reference)			
Positive	0.03 (-0.05, 0.11)	0.521		
Date of HIV diagnosis				
>3 months before starting MDR-TB treatment	1.0 (Reference)			
<3 months before starting MDR-TB treatment	0.01 (-0.06, 0.09)	0.731		
ART				
Yes	1.0 (Reference)			
No	0.00 (-0.07, 0.07)	0.992		
Date of ART initiation				
>1 month before starting MDR-TB treatment	1.0 (Reference)			
<1 month before starting MDR-TB treatment	0.02 (-0.05, 0.10)	0.490		
Co-morbidity (not including HIV)				
Present	1.0 (Reference)			
Absent	-0.001 (-0.08, 0.08)	0.975		
Baseline BMI				
Normal weight (18.5-24.9)	1.0 (Reference)			
Underweight (<18.5)	-0.05 (-0.15, 0.05)	0.317		
Overweight (≥ 25)	-0.12 (-0.23, -0.02)	0.020*		
Baseline Hgb				
Normal (≥ 12 g/dL)	1.0 (Reference)			
Low Hgb (< 12 g/dL)	0.06 (-0.01, 0.14)	0.088		
Baseline K				
Normal (3.5-5.1 mmol/L)	1.0 (Reference)			
Abnormal (<3.5 mmol/L or >5.1 mmol/L)	0.02 (-0.1, 0.1)	0.671		

Table 15. (cont'd)

Patient and Clinical Characteristics	Unadjusted Coef (95% CI)	*P* value	Adjusted Coef (95% CI)	*P* value
Baseline TSH				
Normal (≤5.50 mIU/L)	1.0 (Reference)			
Elevated TSH (>5.50 mIU/L)	-0.1 (-0.3, 0.1)	0.244		
Baseline creatinine				
Normal	1.0 (Reference)			
Elevated creatinine (creat >90 μmol/L)	-0.1 (-0.2, 0.1)	0.215		
Baseline ALT				
Normal	1.0 (Reference)			
Elevated ALT (>35)	-0.01 (-0.1, 0.1)	0.829		
Baseline MDR-TB regimen				
Standardized (Km-E-Z-Eto-Mfx-Trd)	1.0 (Reference)			
Standardized + INH	-0.002 (-0.08, 0.08)	0.968		
Modified regimen (Decreased frequency of Km)	0.05 (-0.1, 0.2)	0.348		
Other modifications	-0.09 (-0.3, 0.1)	0.298		

CI = confidence interval, *p<0.05, **p<0.01, ***p<0.001

Only three variables had a significant effect on HRQOL: starting treatment with a BMI>25, hospitalization and change in relationship status. In the multivariable model, only one patient variable and one clinical variable were found to still be significant: loss of a relationship since the start of treatment and prior hospitalization during MDR-TB treatment. Combining these two variables to the ADR model resulted in the final multivariable model, presented in Table 16 with an adjusted R^2 of 0.51 indicating improved goodness of fit. Once the final model was fitted, each of the patient and clinical variables in the final model remained significant when adjusting for age, sex, HIV and ART status, other co-morbidities, BMI, housing, abnormal laboratory values at baseline, food insecurity, dependents, change in employment, and time on treatment.

Table 16. Final multivariable model presenting the adjusted effect of ADRs and patient and clinical variables on HRQOL during MDR-TB treatment

	Model 1: Multivariable Final Effects Model		**Model 2: Age- and Sex-adjusted Final Effects Model**	
Explanatory Variable	**Effect on HRQOL† Adj Coef (95% CI)**	**p-value**	**Effect on HRQOL† Adj Coef (95% CI)**	**p-value**
Bothersome diarrhea	-0.14 (-0.22, -0.07)	<0.001***	-0.14 (-0.22, -0.07)	<0.001***
Nausea/vomiting	-0.09 (-0.14, -0.04)	0.001**	-0.09 (-0.14, -0.04)	0.001**
Loss of relationship	-0.10 (-0.16, -0.04)	0.001**	-0.10 (-0.16, -0.04)	0.001**
Bothersome peripheral neuropathy	-0.09 (-0.15, -0.03)	0.004**	-0.09 (-0.15, -0.03)	0.004**
Myalgia	-0.07 (-0.13, -0.01)	0.019*	-0.07 (-0.13, -0.01)	0.025*
Tinnitus	-0.06 (-0.11, -0.01)	0.020*	-0.06 (-0.11, -0.01)	0.019*
Any hospitalization during treatment	0.06 (0.01, 0.11)	0.022*	0.06 (0.01, 0.11)	0.021*
Arthralgia	-0.06 (-0.12, -0.005)	0.035*	-0.07 (-0.13, -0.01)	0.027*
Age			-0.06 (-0.12, -0.005)	0.751
Female			0.17 (-0.12, -0.005)	0.521
Constant	0.92 (0.86, 0.97)	<0.001***	0.91 (0.76, 1.05)	<0.001***
Adj R^2	0.51		0.50	

† HRQOL presented as a continuous summary score from 0.176 to 1.00; *p<0.05, **p<0.01, ***p<0.001

Even though both age and sex were not found to be significantly associated with HRQOL, they have been included in the final model 2 (Table 16) to demonstrate that the eight variables significantly related to HRQOL remain significant, even when adjusting for age and sex.

Summary of Aim 3

In summary, multiple linear regression analysis was used to develop a model for determining the effect of ADRs on HRQOL during MDR-TB treatment. The ADRs that had a statistically significant negative impact on HRQOL were GI ADRs, including nausea/vomiting and bothersome diarrhea, ADRs affecting movement, including myalgia, arthralgia and bothersome peripheral neuropathy and tinnitus. The only patient characteristic that was found to be significant in the final model was the loss of a relationship with a significant other during treatment and the only clinical characteristic was hospitalization during treatment. Of these, prior hospitalization was the only variable found to have a positive effect on HRQOL. Further exploration and implications of these findings are presented in Chapter 6.

CHAPTER 6: Discussion & Implications

This final chapter presents an interpretation of the significant findings between patient and clinical characteristics, ADRs, and HRQOL during MDR-TB treatment. The MDR-TB Treatment HRQOL model used to guide the study has been updated according to the findings and study limitations have been presented. Implications for nursing practice, further research and health policy are discussed. An interpretation of the relationship between the Aim 1 covariates and Aim 2 ADRs is presented first, followed by an interpretation of the final HRQOL multivariable model from Aim 3 that addressed the effect of ADRs and other explanatory covariates on HRQOL.

Interpretation of Relationship Between Covariates and ADRs

The purpose of Aim 1 was to describe patient and clinical characteristics in a sample of community-based MDR-TB patients still in the intensive phase of treatment. Patient demographics such as age, sex, education, SES, and HIV status were similar to previous MDR-TB studies conducted in southern Africa (Brust et al., 2013; Jacobs & Ross, 2012; Seung et al., 2009).

Findings of interest in the descriptive analysis of patient and clinical variables included the high burden of HIV co-infection and a high prevalence of baseline laboratory abnormalities. While the 75% prevalence of HIV co-infection in this study was similar to the previous southern African studies, the surprising finding was that over a third of the participants with HIV were diagnosed within three months of their MDR-TB diagnosis. Likely, the cough, chest pain, and other TB symptoms were the presenting illness that led patients to visit the clinic in the first place, and led to the HIV test. This close window of time between HIV and MDR-TB diagnosis reinforces the need for

improved integration between TB and HIV services in high HIV-prevalent populations as patients will have to be monitored for two challenging conditions concomitantly (Karim, Churchyard, Karim, & Lawn, 2009).

Yet, integration of HIV and TB services remains a challenge. Although documentation of HIV status was present for 100% of the participants, many details of the participants' HIV treatment regimen were missing in the MDR-TB medical charts. According to the South African DOH guidelines, all MDR-TB patients should be fast-tracked to initiate ART within two weeks of starting MDR-TB treatment (RSA DOH, 2013a), as TB patients placed on concomitant ART have improved outcomes over those waiting to initiate ART following TB therapy (Karim et al., 2010). In this study, 34% of participants started ART during their MDR-TB treatment, which was comparable to another study in which 31% started ART during MDR-TB treatment (Isaakidis et al., 2011). This study supports the findings of previous research that found no significant difference in ADRs from drug-resistant TB treatment by HIV status (Avong et al., 2015; Brust et al., 2013; Mpagama et al., 2013; Shean et al., 2013; Wu et al., 2013).

Baseline laboratory results were available for the majority of participants. One unexpected finding was the high number of participants with an elevated ALT before starting MDR-TB treatment (*n* = 23/116, 20%). This study found a positive association between increased ALT before starting MDR-TB treatment and total ADRs during treatment. The WHO MDR-TB guidelines suggest caution for patients with baseline hepatic impairment due to the increased risk of ADRs (WHO, 2014a).

There are a number of possible causes for elevated liver function tests at baseline and the author postulates three likely culprits for clinicians to consider. First, the majority of MDR-TB patients are first treated for drug-susceptible TB and three of the first-line anti-tuberculosis medications are potentially hepatoxic (INH, PZA, and EMB) (RSA DOH, 2013a). Secondly, the high rate of HIV co-infection may be associated with underlying, undiagnosed hepatitis (particularily B and C) (Modi & Feld, 2007). Also, ART is potentially hepatotoxic (particularily d4T, EFV, and FTC) (WHO, 2014b). Third, patients may have had excessive alcohol consumption prior to starting treatment. A statistically significant increase in ALT has been found for people who drank greater than 2 drinks per day compared to 2 or less (Liangpunsakul, Qi, Crabb, & Witzmann, 2010), and a multi-province study in South Africa uncovered alcohol misuse in 25% of drug-susceptible TB patients screened (Peltzer et al., 2013). This study was unable to accurately collect data on the number of people who drank alcohol before starting treatment, as only current intake was recorded.

Alcohol-use can be difficult to capture. By asking participants if they currently drink or smoke, this study failed to capture realistic usage. Even MDR-TB studies asking participants if they ever drank alcohol reported surprisingly small numbers at 7.7% (Palacios et al., 2012). One study described beliefs about TB in South Africa and found that even though 95% of respondents understood that TB was infectious, 79% and 74% also believed that it could be caused by cigarettes and alcohol-use, respectively (Edginton et al., 2002). In addition to following clinical provider guidance to quit, this belief may also be related to the cessation of smoking or drinking during treatment (Atkins, Biles, Lewin, Ringsberg, & Thorson, 2010).

While low Hgb levels at baseline were expected since both TB and HIV disease progression can cause anemia, in addition to ART with zidovudine (Bolge, Mody, Ambegaonkar, McDonnell, & Zilberberg, 2007; Cosby et al., 2000; Lee et al., 2006; Shivakoti et al., 2015), there was a surprisingly high number of participants with a Hgb below 10 g/dL at baseline (26%). One of the most unexpected results of this study was the positive association between higher baseline Hgb levels and a greater number of total ADRs. This effect appears to only be present for Hgb<12 g/dL; once the levels fall below 10 g/dL, the relationship is no longer statistically significant. The effect decreases even further with a starting Hgb<8 g/dL. The reason for these findings is unknown.

A significant difference in total number of ADRs per patient was also found between the sexes. These findings support previous research demonstrating an increased risk of ADRs for females (Bloss et al., 2010; Carroll et al., 2012).

Although incidence of default from MDR-TB treatment had been recorded in previous treatment outcome studies (Franke et al., 2008; Gler et al., 2012; Sanchez-Padilla et al., 2014; Toczek, Cox, Du Cros, Cooke, & Ford, 2013), few have measured adherence. Whereas investigations of default often follow up with patients who have not been to their monthly clinic visit for the past two months, an investigation of adherence would include all patients with the attempt to uncover less obvious acts of non-adherence, such as selectively choosing not to take one of the medications without notifying the provider. In this study, 42% reported forgetting to take medications at least once in a while. Unfortunately, the MMAS-8 adherence scale had low reliability in this study. This may indicate that this is not the best adherence scale to use in this

population as another HIV study in South Africa also found low internal reliability for the 4-item version of the scale (α=0.45) (Bhengu et al., 2011).

Measurement of adherence was not the primary outcome in this study, but was included for exploratory analysis. There was a significant association between specific ADRs and decreased adherence in the univariable analysis. In particular, depression and anxiety were found to relate to decreased adherence, yet were the only two ADRs that were not recorded in the medical charts for any of the study participants. Previous MDR-TB studies documented 13-18% incidence of depression and 11-12% incidence of anxiety by psychiatrist diagnosis after ruling out any baseline psychiatric conditions (J. Furin et al., 2001; Vega et al., 2004). For the few studies that documented reasons for default, inability to tolerate ADRs (Van Deun et al., 2004) and lack of patient education on medications (Toczek et al., 2013) point to the inverse association between increased ADRs and decreased adherence.

The MT-SI uncovered a high percentage of ADRs in this study sample. Previous studies documenting the prevalence and incidence of ADRs from retrospective chart reviews have presented likely underreporting of ADRs as an important limitation (Palacios et al., 2012). Unexpected findings included the high frequency of insomnia and changes of vision.

Insomnia was the most prevalent ADR in this study (69%). Although it was not found to be significantly related to HRQOL, for the majority of participants, this symptom bothered them a lot (69%). One of the original hypotheses of this study was that more bothersome symptoms would be associated with a greater reduction in HRQOL, but the

high degree of bother from insomnia and lack of association with HRQOL do not support this hypothesis. This lack of association may indiciate that symptom bother is not the best measure of the symptom experience.

Insomnia is most often attributed to Tz or Mfx. An MDR-TB study in Turkey was the only one found to specifically document nightmares, with 20 cases attributed to the fluoroquinolone, but able to manage this ADR by tapering or changing to morning dosing (Törün et al., 2005).

Although insomnia is a common symptom of both HIV disease and ART (Hudson, Portillo, & Lee, 2008; Reid & Dwyer, 2005), no significant increase in insomnia was found among HIV co-infected participants in this study. But the HIV literature may be able to provide interventions that have improved patient perception of sleep without adding another adjunct medication. This high incidence of insomnia may indicate the need to look at timing of medications. The two medications administered at night, Eto and Trd, are done so in order to allow the patient to sleep through the side effects, but based on the high prevalence of insomnia, this may need to be re-examined. Instead, splitting the daytime dose of Eto and/or Trd should be an option for patients reporting insomnia.

Change in vision is often included in the list of ADRs during MDR-TB treatment to capture the presence of optic neuritis, a rare effect of EMB, but if not caught can lead to permanent blindness. Optic neuritis manifests as pain with eye movement, partial loss of vision and/or alteration in color perception, specifically the inability to differentiate red from green. In this study, an unexpectedly high number of participants (43%) reported

experiencing some change in vision since the start of treatment. Previous MDR-TB studies have reported a much smaller incidence 3% - 6% (Bloss et al., 2010; Jacobs & Ross, 2012).

The author hypothesizes two possible causes for the high number of participants indicating a change in vision: the possibility of photophobia, or light sensitivity from Eto and the possibility of vestibular effects on vision, such as nystagmus, from the Km. Although this was not captured as part of the study, numerous participants indicated during the interview that they experienced the eye pain and blurry vision in bright sunlight. A study conducted among drug-susceptible TB patients indicated the presence of photophobia from treatment (Nolan & Goldberg, 2002). Very little has been written about photophobia during MDR-TB treatment, but one study did record 18 cases of photophobia attributed to Eto (Tupasi et al., 2006). In the FDA warning label for Eto, it is noted that patients may experience blurry vision, loss of vision, and eye pain.

The effect of vestibulococchlear impairment on vision is not often mentioned in the MDR-TB literature. All aminoglycosides have a potential effect on cranial nerve VIII. With vestibular impairment may arise blurry vision, distorted vision and nystagmus. Nystagmus is a documented side effect of Km.

A third, less common possibility is ocular inflammatory disease, often from ocular TB, which was also found to be another cause of visual disturbance among MDR-TB/HIV patients (Mehta, Mansoor, Khan, Saranchuk, & Isaakidis, 2013). The distinction between photophobia, nystagmus, ocular inflammatory disease and optic neuritis is important because optic neuritis would constitute a discontinuation of EMB. It can lead

to permanent damage of the optic nerve and resultant blindness, but can be prevented with prompt discontinuation of EMB.

Interpretation of Effect of ADRs on HRQOL

This study helps to fill the gap of patient-centered outcomes among MDR-TB patients by quantifying the effect of ADRs on HRQOL exclusively among MDR-TB patients. Previous studies included smaller sub-samples of MDR-TB patients among drug-susceptible TB populations and found that MDR-TB patients suffered the greatest decline in HRQOL (Guo et al., 2009; Kittikraisak et al., 2012). Based on unadjusted regression coefficients, ADRs produced the most marked reduction of HRQOL in comparison to patient and clinical variables. This effect on HRQOL supported the study's hypothesis, that an increase in total number of ADRs per patient and the presence of specific ADRs would be associated with lower HRQOL utility scores. This inverse association between ADRs and HRQOL also supported findings in a previous studies demonstrating decreased HRQOL utility scores associated with increased ADRs from ART in HIV samples (Braithwaite et al., 2008; Lalanne et al., 2014).

This study helps fill the knowledge gap on the effect of MDR-TB treatment on HRQOL in a low-resource, high HIV-burden population. The six ADRs that remained significantly associated with reduced HRQOL in the multivariable analysis included: any report of nausea/vomiting, myalgia, arthralgia, or tinnitus, and only the most bothersome diarrhea and peripheral neuropathy. All ADRs and HRQOL were tested for a significant difference by HIV status, but not only was there was no significant difference by HIV status, but ART status and time of ART initiation were all found to be statistically insignificant, as well. More recent HIV studies have demonstrated improved HRQOL

during ART, which may be due in part to the improved tolerability of newer ART regimens (Louwagie et al., 2007; Tomita et al., 2014).

Gastrointestinal ADRs. With 57% of participants reporting nausea/vomiting, this study supports the finding of previous research indicating a frequency greater than 50% for nausea/vomiting during MDR-TB treatment (Bezu et al., 2014; Furin et al., 2001; Malla et al., 2009; Sagwa et al., 2012; Shin et al., 2007; Van Deun et al., 2004). Ethionamide was the suspected causal agent, as was the case in other studies (Chiang et al., 2006; Cox et al., 2007; Tupasi et al., 2006), but only required discontinuation in a single case, which was less frequent than other studies (Carroll et al., 2012; Palacios et al., 2012).

One of the major challenges facing clinicians dealing with a complaint of nausea and vomiting is determining if it is a direct result of treatment or an effect of gastritis. Gastritis is defined as the inflammation of the lining of the stomach, which manifests as abdominal pain and dyspepsia, possibly with nausea and vomiting. Gastritis was not found be significantly related to HRQOL in this study. Serious cases may lead to hematemesis. In both cases the suspected causal agents are Eto or PAS, but the challenge is in determining the adjunct treatment, as a histamine type 2-receptor antagnoist or proton pump inhibitor is more appropriate for the nausea and vomiting associated with gastritis, as opposed to an anti-emetic. In Nepal, all patients were given a gastroprotective agent for gastritis (histamine-2 blocker), but 64% of their sample still developed nausea and vomiting (Malla et al., 2009).

Although diarrhea was the least common ADR among participants (25%), bothersome diarrhea was significantly associated with HRQOL. Not all MDR-TB ADR studies include diarrhea (Singla et al., 2009) or it is combined with nausea/vomiting and gastritis as GI effects (Isaakidis et al., 2012; Joseph et al., 2011; Palacios et al., 2012). For those that did record diarrhea separately, a similar frequency was found (Brust et al., 2013). This study demonstrates its importance as a serious ADR for MDR-TB patients and supports its inclusion in future research and policy.

One promising consideration is that both nausea/vomiting and diarrhea tend to abate with time in MDR-TB treatment (WHO, 2014b), but it is important to still provide aggressive evaluation and treatment, otherwise patients can develop nausea even at the thought of their medications (Acha et al., 2007). For management, an anti-emetic is the first line of management for nausea/vomiting and an anti-diarrheal the first line for diarrhea based on WHO guidelines. The South Africa guidelines indicating that the anti-emetic should be administered 30 minutes before taking the MDR-TB medications (RSA DOH, 2013a). This requires additional patient education and anti-emetics have their own ADR profile, with an increased risk of neurological dysfunction. Foundational studies on Eto have demonstrated improvement of GI ADRs by splitting the dose (Gupta, 1977) and this has further been supported in recent MDR-TB literature (Isaakidis et al., 2012; RSA DOH, 2013a).

Management of nausea and vomiting has been successful in hospitalized patients by dietary modifications and symptom management, but is more difficult in community-based settings (Van Deun et al., 2004). Ethionamide may be given without regard to the timing of meals and Eto has been shown to be best tolerated at

mealtimes. If patients are able to persevere with treatment, GI effects tend to diminish as treatment proceeds.

ADRs affecting movement. The second grouping of ADRs found to be significantly related to reduced HRQOL were the neuro-musculo-skeletal ADRs affecting movement: myalgia, arthralgia, and bothersome peripheral neuropathy. Myalgia was not commonly recorded in ADR studies (Wu et al., 2013). Prior studies documented an incidence of myalgia ranging from 20 – 35% (Brust et al., 2013; Tupasi et al., 2006). This study found a much higher incidence of 50%. One hypothesis is that patients sometimes report generalized body pain (Avong et al., 2015), this is rarely captured in the literature and may be related to myalgia.

Myalgia may be a direct result of the MDR-TB medications or muscle cramping as a result of hypokalemia. One hypothesis for the higher incidence of myalgia in this study is the lack of distinction between peripheral neuropathy and myalgia as peripheral neruopathy can also manifest as weakness while walking (RSA DOH, 2013).

The author also considered the possibility of immune reconstitution inflammatory syndrome, which occurs when HIV patients with a very low CD4 count begin ART and their CD4 count revises, thus activating their immune system and causing widespread inflammation. In addition, muscle aches have been reported as highly prevalent in untreated HIV populations (Hudson, Kirksey, & Holzemer, 2004; Makoae et al., 2005) and as an effect of ART (Lalanne et al., 2014). While this may have contributed to the overall occurrence, this was not a significant cause of the increased percentage as indicated by the non-significant effect of HIV and ART on the presence of myalgia.

For arthralgia, PZA is the main culprit for increased uric acid levels (Datta et al., 2009), followed by EMB, which is felt as joint pain by the patient (Tupasi et al., 2006). The incidence of arthralgia in other African studies ranged from 16 - 58% (Brust et al., 2013; Jacobs & Ross, 2012; Mpagama et al., 2013; Sagwa, Ruswa, Musasa, & Mantel-Teeuwisse, 2013) with comparable results of 44% in this study. Arthralgia is managed by non-steroidal anti-inflammatory drugs (Datta et al., 2009), but several participants in the study were on analgesics, but still complained of joint pain.

ART and HIV disease can cause peripheral neuropathy and this has been shown to be significant for the report of peripheral neuropathy prior to starting treatment (Conradie et al., 2013), but not necessarily increasing the chances of developing peripheral neuropathy during treatment. Peripheral neuropathy is generally well managed either through treatment of contributing co-morbidities, adjunct medication for the neuropathic pain or adjustment of causal medication (Shin et al., 2003). Yet, even with aggressive symptom management, peripheral neuropathy may still be irreversible (Conradie et al., 2013; Scano et al., 2008; Shin et al., 2003).

These ADRs that affect physical functioning have been shown to also impact social functioning and usual activities (Acha et al., 2007). This compounded effect could be a main reason for the significant relationship between myalgia, arthralgia, and peripheral neuropathy on HRQOL, since the EQ-5D HRQOL score incorporates movement, social roles and usual activities into the composite score. In addition, this relationship between movement, social roles and usual activities supports the inclusion of relationship status in the final effects model.

Tinnitus. The third grouping of ADRs significantly associated with HRQOL was the vestibulococchlear symptom of tinnitus associated with damage to cranial nerve VIII. Aminoglycosides, Km in this case, are known to be ototoxic, which includes both hearing disturbance and tinnitus and vestibular symptoms such as dizziness, imbalance, and vertigo. Incidence of tinnitus in this study was 40%, comparable to others studies ranging from 35 - 40% (Bloss et al., 2010; Sagwa et al., 2013).

Of note, hearing loss, considered one of the most serious and disabling ADRs during MDR-TB treatment (Avong et al., 2015; Sturdy et al., 2011), was not found to have a high degree of bother or be related to a significant decrease in HRQOL in the multivariable model. The author postulates that this is due to the proactive management of the clinical staff for this condition. As presented under additional findings, hearing loss was the most commonly reported ADR in the medical charts and had the greatest degree of concordance with patient self-report. Patients are routinely questioned about changes in hearing during their monthly visit at the clinic. Audiology screenings are conducted regularly, which have the ability to detect hearing loss at high frequencies before patients even become symptomatic (Sturdy et al., 2011). Hearing loss was the primary cause of changes to the MDR-TB medical regimen, with Km levels adjusted frequently.

Loss of a relationship. Almost a quarter of the sample ended a relationship with their significant other during MDR-TB treatment. As would be expected, this was associated with a decrease in HRQOL. Stable relationships are associated with an increase in HRQOL (Guo et al., 2009; Tomita et al., 2014). Although this is not a modifiable clinical variable, this study indicates that clinicians should consider the

importance of patient relationships outside the clinical setting. Previous qualitative studies have demonstrated an association between MDR-TB treatment outcomes and the relationship status of patients (Acha et al., 2007; Chalco et al., 2006).

Hospitalization. The variable of hospitalization was added to the medical chart data abstraction form, but it was not originally included as a separate variable in the MDR-TB Treatment HRQOL model used to guide this study. Yet, having been hospitalized at some point during MDR-TB treatment was found to have a statistically significant association with an increased HRQOL score in the mulitivariable analysis. The author postulates that this positive effect was due to patient preference for being treated in the community, with higher HRQOL for patients after being discharged from the hospital. This hypothesis is supported by two bodies of literature. The first is patient preference for decentralized, or community-based care, which allows for family support and is more convenient and less costly to the patient (Horter, Stringer, Reynolds, et al., 2014). The success of community-based treatment is evidenced by improved MDR-TB treatment outcomes, earlier treatment initiation and reduced default from treatment (Gler et al., 2012; Loveday et al., 2015).

The second body of literature demonstrates that HRQOL increases with treatment, as has been shown in HIV studies with ART (Jaquet et al., 2013; Jelsma et al., 2005), and drug-susceptible TB studies (Bauer et al., 2013; Chamla, 2004; Guo et al., 2009; Kruijshaar et al., 2010; Maguire et al., 2009). Patients who were hospitalized during treatment likely had a higher degree of acuity, which may have resulted in a better sense of improved well-being after being discharged for community treatment. This hypothesis also supports the positive finding between slightly lower baseline Hgb

and less self-reported ADRs. There may be an underlying theme of patients who begin MDR-TB treatment at a slightly higher acuity level actually having better self-reported outcomes due to perceived improvement during treatment. Longitudinal data would be necessary to support this theory.

In summary, ADRs were very common during MDR-TB treatment and some ADRs were found to have a negative impact on HRQOL. Current guidelines focus on adjunct medications for ADR treatment, but MDR-TB/HIV patients already have a tremendous pill burden and each new medication introduced has its own side effect profile, such as the potential neurological effects of metoclopramide noted previously. An increase in the number of medications during MDR-TB treatment has been linked to default (Gler et al., 2012). In addition, adjunct medications require additional education on proper dosing, which, based on anecdotal evidence, is rarely provided.

Results in Relation to Conceptual Framework

Three revisions were made to the MDR-TB Treatment HRQOL model. The first was the move of adherence form patient characteristics of the individual to clinical characteristics (Figure 7). This way, individual patient characteristics could still affect adherence, but now the two-way arrow between clinical characteristics and ADRs would allow for changes in adherence to affect ADRs and specific ADRs to, in turn, affect adherence.

The second revision was to include hospitalization as a separate variable under clinical characteristics. It has been renamed “hospital- or community-based” treatment.

This variable remained under clinical characteristics as it was found to have significant association on both ADRs and HRQOL.

The third revision was to change all the lines indicating a relationship between patient characteristics—both individual and environmental—and ADRs and HRQOL from solid lines to dashed lines. In the original study model, using a solid line over a dashed line was meant to indicate strength of association. Originally, the only dashed lines were between the patient variables and the clinical varaibles because there was not a clear association between the each patient variable and each clinical variable. From the findings of this study, the majority of patient variables were not significantly related to either total ADRs or HRQOL, therefore the lines indicating these relationships have been been changed to dashed lines.

The main relationship supported by this study was the linear association between clinical characteristics, ADRs and HRQOL. These are the only arrows that remained solid indicating stronger association between concepts. With HRQOL as the principal outcome of the model, and not overall quality-of-life, the clinical variables and ADRs should have greater importance in this health-related model over the patient variables, and the solid arrows help provide this emphasis.

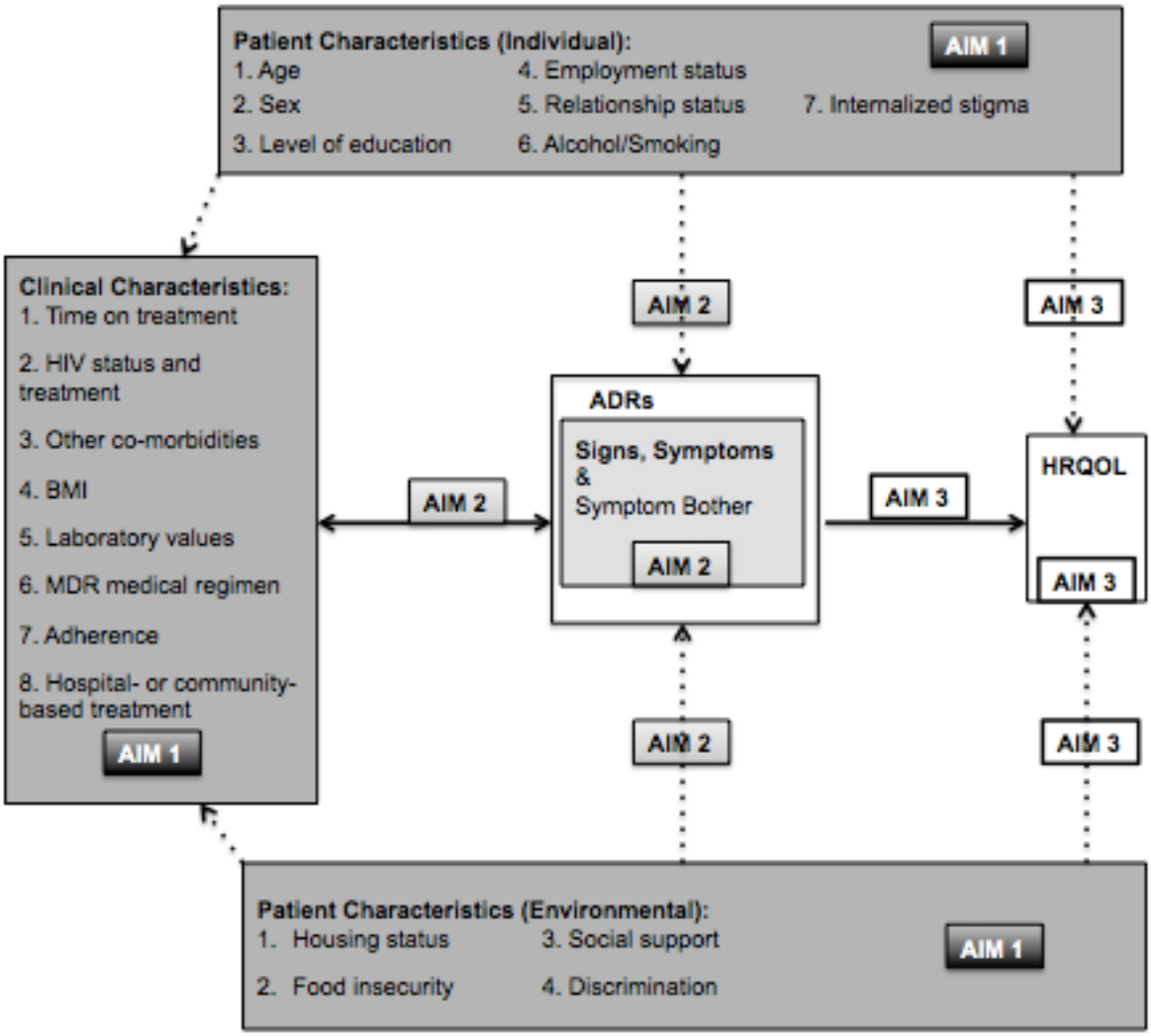


Figure 7. Revised MDR-TB treatment HRQOL model

Study Limitations

The language barriers presented a difficulty in this study. For this reason, the PI hired an RA who was fluent in both *isi*Zulu and English. All instruments were translated into *isi*Zulu and back-translated into English before beginning data collection using a professional translation company in South Africa. The EQ-5D and EQ-VAS were already provided in *isi*Zulu from the EuroQOL group. If the interview was conducted in *isi*Zulu, the RA immediately translated the participant's response into English so the PI

could verify and record the data.

Another limitation was the quality of the MDR-TB medical charts at KDH. All charting is done on paper and there is minimal documentation by the clinical providers and nurses, and often times it is difficult to read. In addition, laboratory results were printed from the NHLS on separate paper and had to be added to the file by hand, as did pharmacy medical administration records, and therefore both were often missing from the charts. Multiple imputation allowed for the inclusion of baseline laboratory variables without diminishing the sample size, but may introduce additional bias into the statisitcal analysis.

With convenience sampling, there was a risk of selection bias. To prevent this, all patients waiting at the clinic were approached for the study. This meant that patients were approached no matter how they appeared, that is, no presumptions were made about whether patients would meet the inclusion criteria based on their appearance. Patients were also approached from clinic opening at 7:30 to closing at 1:30 to prevent the possibility of differences in patients who might come to the clinic early compared to those who arrived near to closing. The only patients who agreed to participate in the study but were not interviewed, were those that did not meet the inclusion criteria. This included patients who were either under 18 years of age, no longer on the intensive phase of treatment or receiving treatment for XDR-TB instead of MDR-TB.

The small sample size was another potential limitation. They study was powered to detect a significant difference in HRQOL utility scores. The study was not powered to detect a significant difference in ADRs by HIV status as this would have required

stratified sampling and a significantly higher sample size.

The study design presented another limitation. With a cross-sectional design, the presence of absence of a symptom at baseline came from patient self-report and there was a risk of recall bias. Another limitation inherent to cross-sectional design is the inability to infer causality between independent variables and HRQOL.

Another possible limitation was the lack of confirmation of MDR-TB status of the study participants via drug sensitivity testing and sputum culture. During the research design process, it was deemed unnecessary to collect culture confirmation of drug-resistance status from the NHLS laboratory results for one important reason. All participants in this study were on second-line MDR-TB treatment, regardless of the source of their MDR-TB diagnosis, and therefore, all were at risk for the same ADRs. Changes in the MDR-TB regimen were made for many participants as drug sensitivity testing and sputum culture results returned from the laboratory, but changes to the medical regimen were not found to be significantly related to ADRs or HRQOL in this study.

Implications for Nursing Practice

This study revealed the high prevalence, high degree of bother, and significant impact of ADRs on MDR-TB patients' HRQOL and adherence to treatment. The South African Nursing Council provides a Scope of Practice (South African Nursing Council, 1991) for registered and enrolled nurses, with enrolled nurses similar to licensed practical nurses in the United States. Enrolled nurses make up the majority of the nursing workforce in South Africa. Both scopes of practice include "observation of

reactions to medication and treatment", "communication by and with a patient in the execution of nursing care", and "promotion of the attainment of optimal health". The registered nurse is further tasked to provide "effective patient advocacy" and to provide "teaching and counseling" for promote health and prevent disease. Therefore, it is the nurses' responsibility to both observe and communicate with the patient in regards to the ADRs he or she is experiencing from the treatment, but to do the same for the effectiveness of the management of the ADRs. This active nursing role has played a key role in the success of the MDR-TB treatment in Peru with treatment success rates of 67% compared to the global average of 50% (WHO, 2014c).

Nursing interventions could include 1) reviewing the medications with the patient to distinguish the adjunct medications from the MDR-TB or ART medications and ensure patients know when to take each medication; 2) asking patients about possible ADRs from a checklist before they sit down with the provider as patients may underreport to the clinical provider (Gonzalez-Gonzalez, Lopez-Gonzalez, Herdeiro, & Figueiras, 2013; Hazell & Shakir, 2012); 3) documenting management of patient's ADRs, including asking the patient self-care methods they are using to help relieve symptoms, as these might prove useful to other patients; 4) providing education and explanation to the patients when they report an ADR; 5) ensuring that baseline laboratory values and symptom assessment have been completed in the medical charts to be able to distinguish a future symptom as an ADR or a pre-existing condition.

Currently, the nursing workflow of an MDR-TB clinic visit includes 1) nurses checking in patients who arrive at the clinic, collecting the sputum samples and the weights, 2) nurses assisting the secretaries to find the medical charts of the arriving

patients and check for completeness of documentation, 3) nurses conducting phlebotomy, and 4) the majority of the nursing staff are translating for the clinical providers since most of the providers do not speak the same language as the patients. With the current system, the patients have no designated time alone with a nurse, yet the effect of nurse-led care has been shown to increase HRQOL in HIV patients (Suzan-Monti et al., 2015) and improve ADR reporting in MDR-TB patients (Farley et al., 2014).

Nurses have the ability to improve the MDR-TB treatment experience for the patient. Nurse-led support groups have demonstrated positive MDR-TB treatment outcomes and reduced default (Acha et al., 2007; Chalco et al., 2006). MDR-TB/HIV patients often have a mistrust of the healthcare system following multiple failed attempts at treatment for susceptible TB (Furin, Isaakidis, Reid, & Kielmann, 2014; Munro et al., 2007) and nursing focus groups have indicated that nurses feel they should give patients more education and support (Motsomane & Peu, 2008). In a study in southern Africa asking HIV patients how they best manage symptoms, adjunct medications were considered most effective, followed closely by seeking help or attending group sessions, primarily with health care providers (Sukati et al., 2005).

Implications for Further Research

There is a great need for further research into effective management of ADRs, especially in a community-based setting. There is a need for both observational and interventional research. Observational studies could answer current gaps such as the effect of the MDR-TB/HIV and adjunct medication pill burden, the effectiveness of adjunct medications, and patients' current level of knowledge about adjunct medication

dosing. Observational studies could also be used to document successful self-care methods patients are already using to manage symptoms between their monthly visits to the clinic and non-pharmacological methods nurses are using, but not recording in the medical charts.

A question that arose during the analysis of the ADRs in the study was the possibility of symptom clusters. As seen in this study, patients rarely present with a single symptom (Miaskowski, Dodd, & Lee, 2004). Further analysis could determine if there is an additive effect between certain symptoms on outcomes such as HRQOL and adherence. Symptoms could be analyzed by body systems, such as GI or musculoskeletal, to determine if the ADRs listed as significant in this study are effecting one another.

There is also a need to conduct a longitudinal study on HRQOL among MDR-TB patients in the continuation phase of treatment to see the effect of treatment over time. Based on the positive relationship between participants who had been hospitalized and now were receiving community-based treatment, the author hypothesizes that a longitudinal HRQOL study would demonstrate a spike in improvement early in treatment once TB symptoms abate, but gradually decline over the 2-year treatment period. In addition, research should be done on patients who have completed MDR-TB treatment to answer questions about the lasting effect of the disease and the treatment. Previous research has uncovered residual lung damage following MDR-TB treatment (De Valliere & Barker, 2004) and posed questions on the long term impact of MDR-TB infection on HRQOL. This also leads to the question of which ADRs are permanent (Padayatchi et

al., 2010), and which may continue to have a lasting effect on HRQOL, long after MDR-TB treatment has finished.

Implications for Health Policy

In 2011, the South African National AIDS Council released The National Strategic Plan on HIV, STIs and TB for 2012 – 2016 in collaboration with the South African DOH (The South African National AIDS Council [SANAC], 2011). One of the four strategic objectives for 2016 is to sustain health and wellness, primarily by a significant reduction in deaths and disabilities from HIV and TB. This study highlights the need for improved documentation and management of ADRs. This study found a high percentage of ADRs using a checklist system for ADR reporting. The 2011 South African DOH MDR-TB guidelines provided a sample form for ADR reporting with an open space for reporting any ADR using general inquiry questioning. Open-ended general inquiry collection of ADRs, or asking questions, such as “are you having any problems with treatment” or “how are you feeling?” provide minimal reporting of ADRs. In an study among HIV patients in South Africa, there was an 87% increase in ADR reporting between general enquiry and a symptom checklist (Allen et al., 2013). There is a great need for standardization of ADR reporting (Avong et al., 2015).

The findings from this study may be generalizable to other low-resource, high HIV-burden populations in sub-Saharan Africa. This study is presented at a time when the WHO has just released its TB strategies for 2025, calling for “integrated, patient-centered care and prevention” to decrease TB deaths by 75% and incidence by 50% (WHO, 2015a).

Contribution to Science

This study specifically addresses the need for increased research on HRQOL among MDR-TB patients in a high HIV burden, low resource setting. The major findings of this study are summarized in Table 17. The study findings demonstrated a reduction in HRQOL utility scores ranging from 0.06 to 0.14 decrement in utility attributable to ADRs. These findings demonstrate a more marked reduction in HRQOL than attributed to ART ADRs in HIV populations (Braithwaite et al., 2008).

This study provides a broader picture of the experience of MDR-TB patients by uncovering a higher incidence of ADRs, such as insomnia and vision changes. In addition, a high degree of discordance between patient self-report and provider documentation of ADRs in the medical charts was discovered.

Table 17. Summary of major findings for each aim of study

Aims	Major Findings
Aim 1	- High degree of food insecurity (*n* = 62/121, 51%)
	- Many patients started ART concomitantly with MDR-TB treatment (*n* = 31/90, 34%)
	- Many patients diagnosed with HIV within three months of starting MDR-TB treatment (*n* = 32/90, 36%)
	- Baseline laboratory abnormalities were common: • Majority of patients started treatment with a Hgb < 12 (*n* = 75/115, 65%) • Many patients started treatment with ALT > 35 (*n* = 23/116, 20%)
Aim 2	- High incidence of ADRs with majority of patients reporting at least one ADR (*n* = 119, 98%)
	- 8.6 ADRs/patient by patient self-report vs. 1.4 ADRs/patient by provider documentation
	- Depression, anxiety and confusion associated with reduced adherence ($p<0.001$)
	- Females and elevated ALT at baseline associated with higher number of total ADRs
Aim 3	- Increased total ADRs associated with reduced HRQOL ($p<0.001$)
	- Six ADRs associated with reduced HRQOL leading to a decrement in utility ranging from 0.06 to 0.14

Conclusion

The primary purpose of this study was to determine which ADRs are most significantly associated with a reduction in HRQOL during MDR-TB treatment. This study supports the findings from previous focus group studies indicating the significantly negative impact of ADRs on patient well-being (Chalco et al., 2006; Horter, Stringer, Venis, & du Cros, 2014; Isaakidis et al., 2013). This study helps fill the gap in the literature identified by the WHO on the impact of anti-TB medication on morbidity and HRQOL. A secondary finding of this study was the high degree of underreporting of

ADRs by providers in the medical charts, which can misrepresent the plight of MDR-TB patients in national and global pharmacovigilance programs (Mehta et al., 2014; Pal, Lienhardt, Olsson, & Falzon, 2012).

APPENDICES

APPENDIX A:

Study Instruments

Patient Interview Questionnaire

A. INDIVIDUAL PATIENT CHARACTERISTICS

Date of interview *(interview)* __ __/__ __/__ __ __ __ (*dd/mm/yyyy)*

Sex *(sex)* ____ *(1=male 2=female)*

1a. What is the highest grade that you finished in school? *(educate)* ____

(0=no formal education, 1= completed some or all primary [from grade 1-7], 2= completed some or all secondary [from grade 8-12 or matric], 3=university or professional, 4=technical school [example: trained as electrician], 5=other, 9=unknown)

1b. Education: specify other *(educate_other)* _____

2a. What was your employment status before getting MDR-TB? *(employ_prior)* ____

(0=unemployed, 1=employed [include full-time, part-time or temporary], 2=retired, 3=student [include full-time or part-time], 4=disabled, 5=other, 9=unknown)

2b. Employment prior: specify other *(employ_prior_other)* _____

2c. Has there been a change in your employment since starting MDR-TB treatment? (*employ_change)* ____ *(0=no change, 1=lost job/forced to leave school, 2=quit job or school, 3=temporary leave from job or school, 4=reduced hours at job or school, 5= other)*

2d. Employment change: specify other (*employ_change_other)* _____

3a. What was your relationship status before getting MDR-TB? *(relation_prior)* ____

(*1=single/never married, 2=married, 3=separated/divorced, 4=widowed, 5=engaged to be married, 6=cohabiting, 7=girlfriend/boyfriend, 9=unknown, 0=other)*

3b. Relationship prior: specify other *(relation_prior_other)* _____

3c. Has there been a change in your relationship since starting MDR-TB treatment? *(relation_change)* ____ (*0=no. 1=yes, 9=unknown)*

3d. Relationship change: specify yes *(relation_change_yes)* _____

3e. How many children live in your household? (that you are responsible for?) *(child)* ____

4a. Do you drink alcohol? *(alcohol)* ____ (*0=no, 1=yes, 9=unknown)*

4b. If yes, how many alcoholic beverages do you drink a week? (*alcohol_amount)* ____

5a. Do you smoke cigarettes? *(smoke)* ____ (*0=no, 1=yes, 9=unknown)*

5b. If yes, how many cigarettes do you smoke a day? *(smoke_amount)* **_____**

Internalized Stigma: [Now we are going to read some statements about how having MDR-TB makes you feel. Please tell us if you agree with the following statements, sometimes agree or disagree with the statements.] *

6a. It is difficult to tell people about my MDR-TB infection *(stigma1)* **____** *(1=agree, 2=sometimes, 3=disagree, 9=unknown)*

6b. I feel guilty (or blame myself) that I have MDR-TB *(stigma2)* **____** *(1=agree, 2=sometimes, 3=disagree, 9=unknown)*

6c. I feel worthless because I have MDR-TB *(stigma3)* **____** *(1=agree, 2=sometimes, 3=disagree, 9=unknown)*

6d. I hide my MDR-TB from others *(stigma4)* **____** *(1=agree, 2=sometimes, 3=disagree, 9=unknown)*

Morisky 8-item Adherence Scale: [Now we are going to ask you some questions about taking your MDR-TB medications. Please answer yes or no.] †

7a. Do you sometimes forget to take your medication? *(adhere1)* **____** (*0=no, 1=yes, 9=unknown)*

7b. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past month, were there any days when you did not take your medicine? *(adhere2)* **____** (*0=no, 1=yes, 9=unknown)*

7c. Have you ever cut back or stopped your medicine without telling your doctor because you felt worse when you took it? *(adhere3)* **____** (*0=no, 1=yes, 9=unknown)*

7d. When you travel or leave home, do you sometimes forget to bring along your medicine? *(adhere4)* **____** (*0=no, 1=yes, 9=unknown)*

7e. Did you take all your medicines yesterday? *(adhere5)* **____** (*0=no, 1=yes, 9=unknown)*

7f. When you feel like your symptoms are under control, do you sometimes stop taking your medicine? *(adhere6)* **____** (*0=no, 1=yes, 9=unknown)*

7g. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan? *(adhere7)* **____** (*0=no, 1=yes, 9=unknown)*

7h. How often do you forget or have difficulty remembering to take all your medicine? *(adhere8)* **____** (*0=Never/rarely, 1=Once in a while, 2=Sometimes, 3=Usually, 4=All the time, 9=unknown)*

B. PATIENT CHARACTERISTICS (ENVIRONMENTAL)

[These next questions are a little more about your home and community. Please answer yes or no.]

8a. Do you have electricity in your home? *(electricity)* **____** (*0=no, 1=yes, 9=unknown)*

8b. Do you have running water in your home? *(water)* **____** (*0=no, 1=yes, 9=unknown)*

8c. Do you have enough food to eat everyday? *(food)* **____** (*0=no, 1=yes, 9=unknown)*

Discrimination [Please answer yes or no to the next 2 statements.] *

9a. Some people treated me differently after I told them I had MDR-TB *(discrim1)* **____** (*0=no, 1=yes, 9=unknown)*

9b. I have not told some people about my MDR-TB out of fear *(discrim2)* **____** (*0=no, 1=yes, 9=unknown)*

Social Support [Now we are going to read 2 more statements, please tell us if the statement is "completely true" for you, "somewhat true", "somewhat false" or "completely false" for you.] *

10a. If I were sick and needed someone to take me to a doctor, I would have someone to take me *(social1)* **____** *(1=completely true, 2=somewhat true, 3=somewhat false, 4= completely false, 9=unknown)*

10b. I feel that there is no one I can share my most private concerns and fears *(social2)* **____** *(1=completely true, 2=somewhat true, 3=somewhat false, 4= completely false, 9=unknown)*

* Revised from (Kalichman et al., 2009); † (Morisky et al., 2008)

MDR-TB Symptom Index*

Interviewer:

"Now we are going to change topics and we are going to read a list of symptoms or health problems that you might be having.

Please tell us whether you have experienced any of these symptoms in the past month?" *(Read list & record YES or NO for each symptom.)*

Have patient look at faces scale. "How much does the (*symptom*) bother you?" "No bother, it bothers me a little, it bothers me, or it bothers me a lot?"

"Did you have the (*symptom*) before you started MDR-TB treatment?

		Mark YES or NO to *(symp_ present)*	No bother *(symp_ bother)*	Bother a little	Bothers me	Bothers me a lot	Mark YES or NO to *(symp_ prior)*
1	Fatigue or loss of energy? *(fatigue)*		1	2	3	4	
2	Feeling dizzy or lightheaded? *(dizzy)*		1	2	3	4	
3	Pain, numbness or tingling in the hands or feet? *(pn)*		1	2	3	4	
4	Trouble remembering or confusion? *(confused)*		1	2	3	4	
5	Nausea or Vomiting? *(nv)*		1	2	3	4	
6	Diarrhea or loose bowel movements? *(diarrhea)*		1	2	3	4	
7	Felt sad, down or depressed? *(depress)*		1	2	3	4	
8	Felt nervous or anxious? *(anxious)*		1	2	3	4	
9	Difficulty falling or staying		1	2	3	4	

	asleep? *(insomnia)*						
10	Skin problems such as rash, dryness, or itching? *(rash)*		1	2	3	4	
11	Headache? *(headache)*		1	2	3	4	
12	Loss of appetite or a change in the taste of food? *(anorexia)*		1	2	3	4	
13	Bloating, pain or gas in your stomach? *(gastritis)*		1	2	3	4	
14	Muscle aches? *(muscle)*		1	2	3	4	
15	Joint pain? *(joint)*		1	2	3	4	
16	Problems with weight loss or wasting? *(weightloss)*		1	2	3	4	
17	Loss of hearing? *(hearing)*		1	2	3	4	
18	Ringing in ear? *(tinnitus)*		1	2	3	4	
19	Changes in vision? *(vision)*		1	2	3	4	
20	Other? *(othersymp)*		1	2	3	4	

* Revised from (Justice et al., 2001)

How have these side effects from MDR-TB treatment affected your life? *(symp_life)*

_____

_____

_____

_____

By placing a tick in one box in each group below, please indicate which statements best describe your own state of health TODAY.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

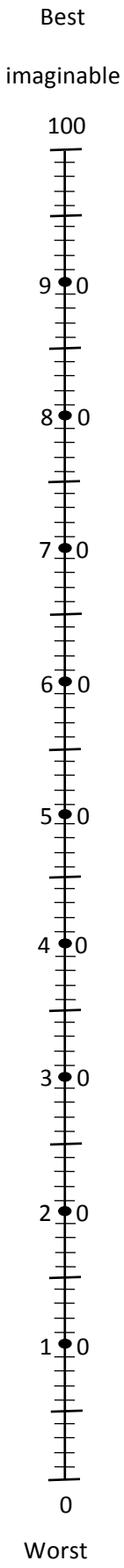
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale, in your opinion, how good or bad your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health



MEDICAL CHART DATA ABSTRACTION TOOL

1a. Age *(age)* (Calculation)
1b. Start Date of MDR-TB Treatment *(date_treat_start)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
2a. Number of times hospitalized during MDR-TB treatment *(hospital_times)* ___
2b. Total length of hospitalization during MDR-TB treatment *(hospital_length)* ___ *(0=never hospitalized, 1=less than or equal to 1 week, 2=greater than 7 days, but less than or equal to 1 month, 3=greater than 1 month, 9=unknown)*
2c. Time on Treatment *(time_treat)* (Calculation)
3a. HIV/AIDS *(hiv_status)* ____ *(0=no, 1=yes, 2=not tested, 9=unknown)*
3b. HIV/AIDS diagnosis date *(hiv_date)* __ __/__ __ __ __ *(mm/yyyy)*
3c. Receiving ARVs *(hiv_arv)* ____ *(0=no, 1=yes, 9=unknown)*
3d. ARV start date *(arv_start)* __ __/__ __ __ __ *(mm/yyyy)*
3e. ARV Regimen *(arv_regimen)* ____ (*1 = TDF, 3TC, EFV, 2 = TDF, 3TC, NVP, 3 = d4T, 3TC, EFV, 4 = Atripla (EFV/TDF/FTC), 5=other, 9=unknown)*
3f. ARV: specify other *(arv_regimen_other)* _____
3g. CD4 count at MDR-TB treatment initiation *(cd4_start)* _____
3h. Date of CD4 count at MDR=TB treatment initiation *(cd4_start_date*) __ __/__ __ __ __ *(mm/yyyy)*
3i. Most recent CD4 count *(cd4_now)* _____
3j. Date of most recent CD4 count *(cd4_now_date*) __ __/__ __ __ __ *(mm/yyyy)*
3k. Viral load at MDR-TB treatment initiation *(viral_start)* _____
3l. Date of viral load at MDR-TB treatment initiation *(viral_start_date)* __ __/__ __ __ __ *(mm/yyyy)*
3m. Most recent viral load *(viral_now)* _____
3n. Date of most recent viral load *(viral_now_date)* __ __/__ __ __ __ *(mm/yyyy)*
Co-morbidities prior to enrollment: (For each of the following, record: 0=no,1=yes, 9=unknown)
4a. Renal/Genito-Urinary Disease *(comorbid_renal)* ___ **--> 4b. specify** *(renal_specify)* _____
4c. Cardiovascular Disease *(comorbid_cardio)* ___ **--> 4d. specify** *(cardio_specify)* _____
4e. Nervous System Disorder *(comorbid_neuro)* ___ **--> 4f. specify** *(neuro_specify)* _____
4g. Musculoskeletal Disorder *(comorbid_musculo)* ___ **--> 4h. specify** *(musculo_specify)* _____
4i. Psychiatric Disorder *(comorbid_psych)* ___ **--> 4j. specify** *(psych_specify)* _____
4k. Liver Disease *(comorbid_liver)* ___ **--> 4l. specify** *(liver_specify)* _____
4m. Skin Disorder *(comorbid_skin)* ___ **--> 4n. specify** *(skin_specify)* _____
4o. Respiratory Disease (not including TB) *(comorbid_resp)* ___ **--> 4p. specify** *(resp_specify)* _____
4q. Diabetes (DM) *(comorbid_diabetes)* ___ **--> 4r. specify** *(diabetes_specify)* _____
4s. Other *(comorbid_other)* ___ **--> 4t. specify** *(other_comorbid_specify)* _____
5a. Weight at MDR-TB treatment initiation *(kilograms) (weight_start)* __ __ __

5b. Date of weight at MDR-TB treatment initiation *(weight_start_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
5c. Height at MDR-TB treatment initiation *(centimeters) (height_start)* __ __ __
5d. BMI at MDR-TB treatment initiation *(bmi_start)* (Calculation)
5e. Most recent weight (kg) *(weight_now)* __ __ __
5f. Date of most recent weight *(weight_now_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
5g. Most recent BMI *(bmi_now)* (Calculation)
6a. Laboratory Results at MDR-TB treatment initiation, date specimen collected *(lab_start_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
6b. Potassium (K or K+) *(k_start)* ____
6c. TSH *(tsh_start)* ____
6d. Creatinine (Cre) *(creat_start)* ____
6e. Creatinine Clearance *(creatclear_start)* (Calculation)
6f. Hemoglobin (Hb or Hgb) *(hgb_start)* ____
6g. ALT *(alt_start)* ____
6h. Potassium (K or K+) *(k_now)* ____
6i. Potassium (K or K+) date *(k_now_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
6j. TSH *(tsh_now)* ____
6k. TSH date *(tsh_now_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
6l. Creatinine (Cre) *(creat_now)* ____
6m. Creatinine (Cre) date *(creat_now_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
6n. Creatinine Clearance *(creatclear_now)* (Calculation)
6o. Hemoglobin (Hb or Hgb) *(hgb_now)* ____
6p. Hemoglobin (Hb or Hgb) date *(hgb_now_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
6q. ALT *(alt_now)* ____
6r. ALT date *(alt_now_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
7a. Audiology results at MDR-TB treatment initiation, date of test *(audio_start_date)* __ __ /__ __ *(mm/yy)*
7b. Results: *(audio_start)* _____
7c. Most recent audiology results, date of test *(audio_now_date)* __ __ /__ __ *(mm/yy)*
7d. Results: *(audio_now)* _____
7e. Additional Audio notes *(audio_notes)* _____
MDR-TB Medical Regimen: (Km=Kanamycin, Mfx=Moxifloxacin, Eto=Ethionamide, E=Ethambutol, Z=Pyrazinamide, Tz=Terizidone)
8a. Standard Regimen (Km, Mfx, Eto, E, Z, & Tz) *(mdr_regimen)* ___ *(0=no, 1=yes, 9=unknown)*
8b. If no, what is the difference *(mdr_regimen_diff)* _____
8c. Any changes to MDR-TB regimen since initiation *(mdr_regimen_change)* ___ *(0=no, 1=yes, 9=unknown)*
8d. If yes, record change in MDR regimen *(mdr_reg1_change)* _____
8e. Record date of change *(mdr_reg1_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
8f. Reason for change in regimen *(mdr_reg1_reason)* _____
8g. If yes, record change in MDR regimen *(mdr_reg2_change)* _____
8h. Record date of change *(mdr_reg2_date)* __ __/__ __/__ __ __ __ *(dd/mm/yyyy)*
8i. Reason for change in regimen *(mdr_reg2_reason)* _____

Adjunct Medications

9a. Pyridoxine/B6 *(pyridoxine)* **___** *(0=no, 1=yes, 9=unknown)*

9b. Tryptanol/Amitryptiline *(tryptanol)* **___** *(0=no, 1=yes, 9=unknown)*

9c. Haloperidol *(haldol)* **___** *(0=no, 1=yes, 9=unknown)*

9d. Panado *(panado)* **___** *(0=no, 1=yes, 9=unknown)*

9e. Name of other adjunct medication *(adjunct1)* **_____**

9f. Reason for medication *(adjunct1_reason)* **_____**

9g. Name of adjunct medication *(adjunct2)* **_____**

9h. Reason for medication *(adjunct2_reason)* **_____**

9i. Name of adjunct medication *(adjunct3)* **_____**

9j. Reason for medication *(adjunct3_reason)* **_____**

10a. Document any symptoms recorded during the MDR-TB treatment initiation intake interview *(intake_symptoms)* **_____** *(0=no symptoms recorded), Circle all that apply:*
1=Loss of appetite, 2=Loss of weight, 3=Abdominal pain, 4=Diarrhea, 5=Vomiting, 6=Other

10b. Specify other symptoms at treatment initiation *(intake_symp_other)*

_____
_____

10c. Were any symptoms recorded in the medical chart since the start of treatment? *(chart_symptoms)* **___** *(0=no, 1=yes, 2=already recorded in this questionnaire, 9=unknown)*

10d. If yes, document any symptoms recorded in the medical chart since the start of treatment (include dates and actions taken) *(chart_symptoms_specify)*

_____

11. General Comments *(comments)*

Field notes or additional data that was not specified in the data collection form. *****Please include dates of clinic visits to look up laboratory data on the NHLS system*****

_____
_____

Interview Response Guide

For Symptom Index

Scale:

It doesn't bother me 1	It bothers me a little 2	It bothers me 3	It bothers me a lot 4

APPENDIX B:

Study Consent Form

Informed Consent Form

Title of the research project: Signs and symptoms associated with adverse drug reactions and health-related quality of life during multidrug-resistant tuberculosis treatment.

Purpose of the study. You are being asked to take part in a research study about the side effects of the MDR-TB (multidrug-resistant tuberculosis) treatment that you are receiving.

Procedure. If you agree to take part in this study, we will interview you by asking you to answer some questions. The interview will take about 30 minutes and can be done in English or isiZulu. The researchers will also gather some information about you and your medical treatment from your medical records.

Benefits. Although you may not benefit from taking part in this study, the information you share may help nurses and doctors identify side effects related to MDR-TB treatment in the future.

Risks. The risks of taking part in this study are small. Some of the questions may upset you. We will take breaks or stop the questions if necessary. You may stop taking part at any time without penalty or loss of benefits.

Confidentiality. Information about you will be kept private to the full extent allowable by law. Only code numbers will identify you on the survey. We will never refer to you by your name, or other identifying information, when discussing or writing about this study. Data will be stored in a password-protected website through Michigan State University in the United States for at least three years after the close of the study. Only members of the research team and the MSU Institutional Review Board will have access to the data.

Your Rights. Taking part in this study is voluntary, you may choose not to take part at all, or you may refuse to answer any of the questions or stop taking part at any time. You may request to take a break during the questions. If you do not want to take part in this study, it will have no effect on your regular health care at this clinic.

Costs and Compensation. There is no cost to you for taking part in this study. At the end of the questions you will be given a 10 Rand airtime voucher for your time and effort.

This study has been ethically reviewed and approved by the UKZN Biomedical Research Ethics Committee.

Contact Information: If you have any concerns or questions about this research study, please contact the lead researcher or the UKZN Biomedical Research Ethics Committee or the Michigan State University Human Subject Protection Program, with all contact information following:

Ana Maria Kelly, BSN, RN, PhD Student
Michigan State University College of Nursing, United States
South African mobile phone number: +27(0)79 354 1499;
E-mail: Ana.Kelly@hc.msu.edu

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Or you may contact:

MSU Human Subject Protection Program in the USA

The Michigan State University's Human Research Protection Program

Tel: 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at: 408 W. Circle Dr., Room 207, Olds Hall, MSU, East Lansing, MI 48824 USA.

Is it okay to proceed with the questions and review of your medical records?

If yes, check here □

APPENDIX C:

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APPENDIX D:

Explanation of Data Transformation

Date of birth was transcribed from the medical charts. Participant age ranged from 17 – 63 (*mean* = 33.1, *SD* = 8.8). Age was then transformed into a categorical variable for the final analysis, based on the WHO age grouping. Participant's sex was confirmed during the medical chart data abstraction. The sample was evenly distributed between females (*n* = 62, 51.2%) and males.

Participants were asked the highest grade they completed in school. All participants had completed at least some primary school. Level of education was fairly homogenous in the sample. The majority of participants had completed some secondary schooling (*n* = 103, 85.1%). Only 10 participants stopped at the primary school level (8.3%) and eight had continued beyond the secondary level (6.6%). Since there was very little variability in level of education in the sample, this variable was not used in the final analysis.

All categories for employment status were considered mutually exclusive and participants were asked to select which category best described their situation including: (a) unemployed (including caring for home), (b) employed (full-time, part-time, or temporary), (c) retired/pensioner, (d) student (full-time or part-time), and (e) disabled. None of the participants classified themselves as disabled and only one participant classified himself as a pensioner, which was merged under unemployed. Just under a third of the sample was unemployed (*n* = 37, 30.6%) at the start of treatment, with the remaining participants combined under employed/student. Participants were asked to note any change in their employment status since the start of MDR-TB treatment. Half

of the participants (*n* = 36/72, 50%) working at the start of treatment were no longer employed by the time of the interview.

The majority of participants (*n* = 98, 81%) described themselves as being in a relationship, with 27 either married, engaged or cohabitating and 71 had a boyfriend or girlfriend, but were not living together. The remaining 23 participants (19%) were classified as single (never married, divorced or widowed).

The majority experienced no change in their relationship status from the start of treatment until the time of interview (*n* = 92, 76%). For 20 participants (16.5%), their relationship ended during MDR-TB treatment. This dichotomous classification, change versus no change in relationship, was used for the analysis in Aim 2. As part of relationship status, participants were also asked if they had any dependents. The results were dichotomized into no children and one or more.

Numerous participants required clarification with the question of alcohol or tobacco cigarette use, asking if this referred to the current situation or before treatment. The questionnaire only recorded current situation, so the study did not account for the majority of respondents who noted that they had stopped drinking or smoking at the start of treatment. Therefore, this question did not accurately capture the use of alcohol or tobacco substances in this sample, as alcohol- and tobacco-use before treatment could have an impact on treatment variables, such as baseline liver enzymes. Only 11 (9.1%) participants indicated that they still drank alcohol and 13 (10.7%) that they still smoked cigarettes. The mean number of drinks per week was 5.3 (*SD* = 2) and

cigarettes per day was 3.7 (*SD* = 0.47). Due to this probable underreporting, substance use was not included in the final analysis.

The four questions taken from the Internalized AIDS Stigma scale were outlined in Chapter 4 and are included in the patient interview instrument in Appendix A. The three possible responses: agree, sometimes, or disagree were collapsed into dichotomous results by combining agree and sometimes agree resulting in scores ranging from 4 (indicated the presence of stigma in all four questions) to 0 (felt no stigma). This was the same method followed by the authors of the original 6-item scale. If participants indicated that they experienced stigma outlined in all four questions, this was classified as "high" stigma.

Internal reliability for the internalized stigma scale was measured using Cronbach's alpha. The four items produced an α = 0.57 in this study, compared to 0.73 reported by the instrument authors for the original six-item questionnaire and 0.67 if one item was deleted. The original scale authors suggested an abbreviated version should have limited impact on the internal consistency, but this was not found to be the case. This may have been due to a lower sample size than the original study and revision of the scale wording from HIV to MDR-TB.

The eight items to address participants' current level of adherence to MDR-TB treatment over the past month in the MMAS-8 were outlined in Chapter 4 and are also included with the instruments in Appendix A. The first seven items were answered yes or no and the final question had five possible answers: never/rarely, once in a while, sometimes, usually, and all the time. The response for the final question was collapsed

into never/rarely indicating a no and an answer of any of the other four responses coded as a yes. For six of the questions, a no resulted in a score of 1 and a yes in 0, and the other question was reverse coded with a yes resulting in a score of 1, to allow for compilation of a total score. Highly adherent patients were identified with a score of 8, medium adherence with a score of 6 to <8, and low adherence with a score of <6, based on the MMAS-8 scoring guidelines.

Even though the majority of participants fell into the 'medium adherence' category (*n* = 58, 47.9%), most of the participants classified as medium adherence scored a 7 (34/58, 58.6%), as opposed to a 6. The question that dropped their score from an 8 to a 7 was "do you feel hassled by having to take medications every day". Many respondents agreed that it was a hassle to take the medications every day, but they still took the medications. The internal consistency for the 8-item scale in this study was low at α = 0.62. This was similar to the α = 0.61 reported by another study conducted in a HIV-positive population in KwaZulu-Natal.

Adherence was listed in the MDR-TB Treatment HRQOL model as an explanatory variable for ADRs and HRQOL. During data collection, it became evident that the ADRs were having an effect on adherence. Therefore, the direction of this relationship has been changed in the final analysis. Adherence was not included in the model building analyses in Aim 2 and 3, but instead analyzed separately as a dependent variable in Aim 2. A summary of the data transformation for each patient characteristic is presented in Table 5.

To assess SES, participants were asked about housing and food. Out of the 121 participants, 22 (18.2%) did not have running water and 12 (9.9%) were without electricity. Only 8 out of 121 (6.6%) participants were without both electricity and running water in their home. Food insecurity was more common. The single question: "do you have enough food to eat every day?" was used to measure the more severe form of food insecurity, lack of quantity, as opposed to lack of choice. The majority of participants, 62 (51.2%) did not have enough food to eat every day.

The final two patient variables in the MDR-TB Treatment HRQOL model were discrimination and social support. Two questions to assess discrimination and two to assess social support were adopted from the Kalichman study to validate the stigma scale and were asked separately. For both variables, if participants answered yes to both questions, they were considered to have high discrimination and high social support. Almost all participants felt they had social support, 116 (96%), so this variable was not included in the Aim 2 and 3 analyses. Only 22 (18%) participants answered positively to both questions of discrimination.

There were seven clinical characteristics outlined in the MDR-TB Treatment HRQOL model used to guide this study. For three of the participants, the full medical charts were missing, so for some of the clinical variables, the total sample size was reduced to 118. These participants were still included in the study because it was possible to collect some of their clinical data from the NHLS electronic medical record and the clinic MDR-TB register. HIV status was considered one of the seven clinical characteristics, but due to its potential importance in the analysis, the other six

characteristics have been stratified by HIV status for the analysis in Aim 1. Significant differences were calculated using chi-square, just as with the patient variables.

HIV status was documented in the medical chart for all 121 participants. A number of additional variables were recorded for the 90 (74.4%) participants who were co-infected with HIV. Date of HIV diagnosis was recorded in 78/90 (86.7%) medical charts and of these, 32/78 (41%) were diagnosed with HIV less than three months before starting their MDR-TB treatment.

Mention of ART status was routinely documented and available in all 90 of the medical charts, with 79/90 (87.8%) on ART. For those not on ART, there was often a clinical provider note to start them on treatment shortly. The most common ART regimen was a fixed-dose combination pill of EFV/TDF/FTC (57/79, 72.2%), followed by a similar regimen of three separate pills of EFV, TDF, and lamivudine (3TC) (5/79, 6.3%). Of the 79 participants on ART, the majority was started on therapy less than one month prior to the start of MDR-TB treatment (43/79, 54.4%), with 12 starting ART before MDR-TB treatment and 31 during.

HIV viral load was included on the questionnaire, but this value was found in less than five medical charts and was therefore not included in the final analysis. CD4 count was more routinely documented with 23/90 (25.6%) participants having a documented CD4 count during MDR-TB treatment, but this still only comprised a quarter of the medical charts. For those documented, the average CD4 during MDR-TB treatment was relatively high (*mean* = 430), but with a high degree of variability between

participants (*SD* = 249.5). Due to the high number of missing values, CD4 count was also removed from the final analysis.

As part of the inclusion criteria for the study, all participants were required to be in the intensive phase of MDR-TB treatment (typically the first 6 – 8 months of treatment). Any patients who had completed taking the injections were excluded from the study. The number of days on MDR-TB treatment was calculated from the start of treatment listed in the medical chart to the time of the interview. If the patient had initiated MDR-TB treatment before arriving to KDH, this was used as the start date. The mean number of days on MDR-TB treatment was 120.3 days (*SD* = 58.8, *range* = 46 – 340), or approximately four months. Participants were well dispersed across time on treatment, with 18.2% in month 2, 21.5% in month 3, 24% in month 4, 23.1% in month 5, and 13.2% in month 6 or beyond. For the analysis in Aim 2, time on treatment was further collapsed into a dichotomous variable based on the mean of 120 days on treatment, which was labeled as: earlier in the intensive phase of treatment (≤120 days) or later in treatment (>120 days).

As part of MDR-TB treatment, hospitalization was also recorded from the medical chart. All participants in the study were receiving community-based treatment through the clinic, but 46 (38%) had been hospitalized at some point during the treatment. Length of hospital stay and number of times hospitalized were included on the questionnaire, but the medical charts rarely provided these details, therefore it was only possible to capture a dichotomized response: hospitalized at some point during MDR-TB treatment or not hospitalized.

Before starting treatment, all MDR-TB patients at KDH undergo a physical examination, their medical history is taken, and baseline laboratory exams and audiology are conducted. Of the 118 complete medical charts, 29 (24.6%) had a documented co-morbidity besides HIV. Co-morbidities present at baseline were documented by the admitting clinical provider in the medical chart by body system. The most common co-morbidity was visual impairment (*n* = 8), followed by hearing impairment (*n* = 7), a dermatological condition such as pruritus or hyperpigmentation (*n* = 7), peripheral neuropathy (*n* = 6), diabetes mellitus (*n* = 4), hypertension (*n* = 3), epilepsy (*n* = 2), asthma (*n* = 2), arthralgia (*n* = 2), and depression (*n* = 1). Although there were no renal or hepatic co-morbidities documented at baseline, there were abnormal lab values at baseline noted below. Since very few participants had a documented co-morbidity, this variable was collapsed into a dichotomous response: co-morbidity present or absent.

Weight was taken at baseline and at each monthly clinic visit. It was used for weight-based dosing of the MDR-TB regimen as well as to indicate successful treatment while waiting for the sputum culture results to convert to negative. Weight was recorded in all 118 (100%) of the available medical charts. Height was only documented in 108/118 (91.5%) of the charts, which limited calculation of BMI. For the 108 participants with a documented height, the mean BMI at the start of treatment was normal at 21.8 (*SD* = 4.5, *range* = 15.6 – 39.8). At the time of the interview, BMI remained almost the same at 22 (*SD* = 4.3, *range* = 14.8 – 38.8). To include BMI in the multivariable model building analyses in Aim 2 and 3, the missing BMI values were imputed, with the statistical process explained in Aim 2.

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