PREVALENCE AND RISK FACTORS OF ADVERSE EVENTS DURING TREATMENT OF DRUG RESISTANT TUBERCULOSIS IN A SETTING OF HIGH HUMAN IMMUNODEFICIENCY VIRUS CO-INFECTION IN NAMIBIA: 2009-10

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A mini-thesis submitted in partial fulfillment of the requirements for the degree of Masters in Public Health at the School of Public Health, University of the Western Cape, South Africa

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Key words

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Adverse Events

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TB/HIV Co-infection

TB and HIV treatment

Drug Resistant Tuberculosis (DR-TB)

Second-line TB medicines

TB medicine safety

Namibia

Abbreviations

-ve	Negative
+ve	Positive
95% CI	95% Confidence Interval
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
AM (AMK)	Amikacin
AMX/CLV	Amoxicyllin/ Clavulanate
Anti-TB	Anti-tubercular
ART	Antiretroviral Therapy
ARV	Antiretroviral (medicine)
AZT	Zidovudine
CLR	Clarithomycin
CM	Capreomycin
CNS	Central Nervous System
CS	Cycloserine
D4T	Stavudine
EFV	Efavirenz
EPTB	Extra Pulmonary TB
ETO	Ethionamide
GIT	Gastrointestinal
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IQR	Inter-quartile range
KM	Kanamycin
LFX	Levofloxacin
MDR	Multi-drug resistant
NTCP	National Tuberculosis Control Programme
NVP	Nevirapine
OFX	Ofloxacin
OR	Odds Ratio
p	p value
PAS	Paraamino salicylic acid
PDR	Poly-drug resistant
PTB	Pulmonary TB

PTH	Prothionamide	SM	Streptomycin
RFB	Rifabutin	SPX	Sparfloxacin
RMP	Rifampicin	TB	Tuberculosis
RR	Relative Risk	TDF	Tenofovir
SD	Standard deviation	XDR	Extensive-drug resistant

Declaration

I declare that ***Prevalence and Risk Factors of Adverse Events During Treatment of Drug Resistant Tuberculosis in a Setting of High Human Immunodeficiency Virus Co-Infection in Namibia: 2009-10*** is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

EVANS LUVAHA SAGWA 25th of February 2012

Signed: 

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ABSTRACT

Introduction

Namibia is currently coping with a dual burden of human immunodeficiency (HIV) and HIV-associated tuberculosis (TB). In 2010, HIV prevalence was 18.8%, the TB case notification rate was 634 per 100,000 population, while TB/HIV co-infection was 58% in 2009. There were 372 reported cases of drug-resistant TB (DR-TB) in 2009.

This study assessed the prevalence, profile and outcome of adverse events (AEs) associated with the treatment of DR-TB, and risk factors for the adverse events.

Methodology

The researcher used a cross-sectional design. Data was collected from the treatment records of all patients treated for DR-TB (N = 59) at the study facility between January 2008 and February 2010. Descriptive statistics were used to describe the frequency of the adverse events and logistic regression to analyse the association between possible risk factors and (specific) adverse events, with stratification (sub-group analysis) and multivariate analysis to adjust for measured confounders. Results of logistic regression analysis are reported as odds ratio (OR), 95% confidence interval (CI) and p-value, where $p<0.05$ was considered to be statistically significant.

Results

A total of 141 adverse events were experienced by 90% (53/59) of patients in the sample. HIV-associated TB occurred in 31 (53%) of the sample. The prevalence of gastrointestinal tract (GIT) adverse events was 64%, tinnitus 45%, joint pain 28% and

decreased hearing 25%. Abdominal pain, rash, nausea, decreased hearing and joint pain were found to be more common in people living with HIV than in HIV-negative patients.

Moderate-to-severe adverse events were mostly experienced after four weeks of DR-TB treatment (OR 6.4; 95% CI 1.6 – 25.6, p= 0.01). Drug-resistant TB patients who were co-infected with HIV were more prone to experiencing three or more adverse events (OR 3.9; 95% CI 1.2 – 13.6, p= 0.03). Patients treated with zidovudine-based ART were at an increased risk of experiencing nausea (OR 7.5; 95% CI 1.1 -51.5, p=0.04). Females were associated with an increased risk of skin rash (OR 15.7; 95% CI 1.7 – 143.7, p=0.01). The use of cycloserine-based DR-TB regimens was associated with joint pain (OR 6.5; 95% CI 1.6 – 25.8, p=0.01), while the risk of ototoxicity was associated with the use of amikacin-containing regimens (OR 12.0; 95% CI 1.3 – 111.3, p=0.03).

Conclusions

Adverse events were found to be more common among patients treated for DR-TB (90% prevalence), particularly during the intensive phase of TB therapy. Most of these adverse events were mild and tolerable. Some adverse events were more common among DR-TB patients who were co-infected with HIV than in HIV-negative patients. The characteristics and risk factors of the serious adverse events need further research. The use of cycloserine-based DR-TB regimens was associated with joint pain. Findings of the risk factor analysis are inconclusive because of the small sample size, which severely limited the power of the study.

Clinicians should invest more time in the prevention and management of adverse events, and should pay greater attention to the needs of HIV co-infected DR-TB patients who are using second-line anti-TB medications, especially those who are concomitantly undergoing treatment using antiretroviral medicines.

1. INTRODUCTION

Background

The global and national epidemiology of tuberculosis

Infection by *Mycobacteria tuberculosis* continues to be a growing global public health problem that afflicts large numbers of human populations across the globe, and particularly those in sub-Saharan Africa, including Namibia (WHO, 2008a). According to the World Health Organization's (WHO) Global Tuberculosis Control Report of 2008, the global incidence of TB was estimated to be 9.2 million new cases in 2006 (i.e. 139 new cases per 100,000 population), with Africa registering the highest incidence per population of 363 per 100, 000 people (WHO, 2008a: 3). The 2007 data relating to Namibia's TB profile which is available in the WHO TB database, cites Namibia's 2007 TB incidence as high, with 767 cases per 100,000 population, which was more than twice as high the average incidence for other countries in the African region. Namibia's TB mortality rate was reported to be equally high in 2007 (102 cases per 100,000 population), while the HIV and TB co-infection was 67 percent (WHO, 2009a).

The 2009 Global TB Control: WHO Report indicates that Namibia ranked second (after Swaziland) as the country with the second highest TB case notification rate. This information is based on the TB notification data of 2006 (see Figure 1.1 below). In spite of this, Namibia is not considered to be among the 22 high TB burden countries because of its small population, which was estimated in 2008 to be 2,065,224 (Central Bureau of Statistics, 2006). In reality, this results in low absolute numbers of patients with TB when one compares Namibia to the other more densely populated countries of the world.

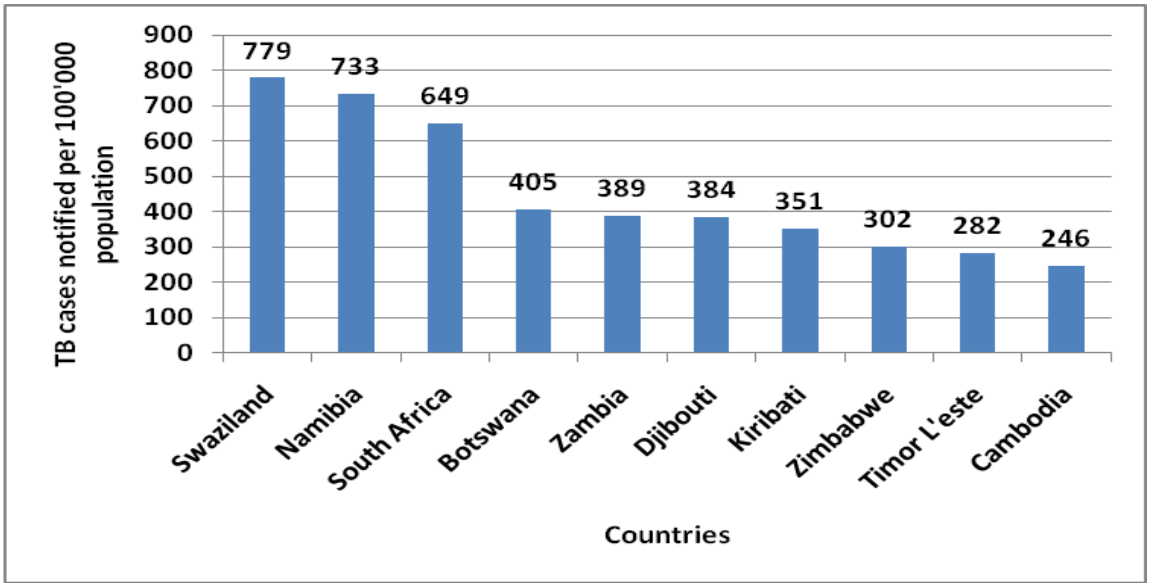


Figure 1.1: The ten countries with the highest TB case notification rates in the world

Source: WHO, 2009

The burden of tuberculosis disease in Namibia peaked in the year 2004, when the case notification rate stood at 822 cases per 100,000 population. But since 2004, this rate has steadily declined because of the number of the well-designed and focused TB prevention, treatment and control measures that have been implemented by the National Tuberculosis and Leprosy Control Program (MoHSS, 2010) as shown in Figure 1.2 below.

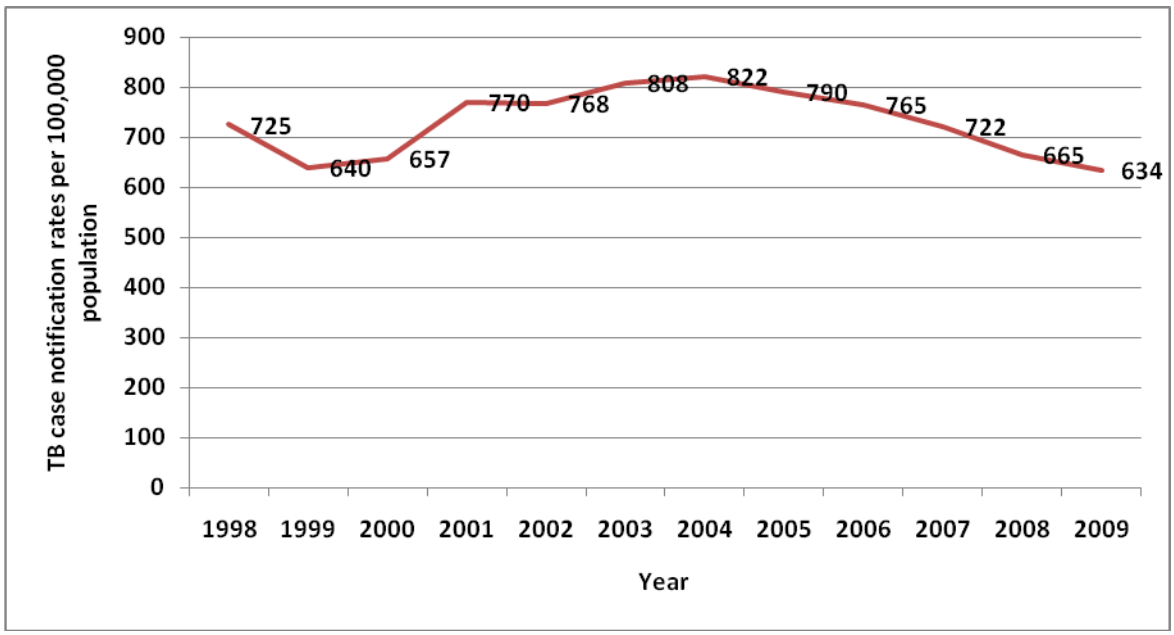


Figure 1.2: Trends in TB case notification rates, 1998-2009, Namibia

Source: MoHSS, 2010. [Note the slight difference in the MoHSS and WHO figures for 2006.

The burden of drug resistant tuberculosis disease

The specter of drug-resistant TB poses a serious threat to public health throughout the world, but especially in southern Africa. There were an estimated 0.5 million cases of MDR-TB globally in 2007, with South Africa accounting for 16, 000 of these cases (WHO, 2009b: 2).

According to the World Health Organization's guidelines on the treatment of tuberculosis (WHO, 2010a), the resistance of the mycobacterium to anti-tuberculosis chemotherapy can range from resistance to one drug (mono-resistance) to resistance to more than one anti-TB drug, other than both isoniazid and rifampicin (poly-resistance)

to multidrug resistance, which is the resistance to both of the two most commonly used anti-TB drugs (rifampicin and isoniazid). While multi-drug-resistant tuberculosis (MDR-TB) is caused by bacteria that are resistant to at least isoniazid and rifampicin (the two mostly effective anti-TB drugs), extensively drug-resistant TB (XDR-TB) is caused by bacteria that are resistant to isoniazid and rifampicin as well as to any fluoroquinolone and any of the second-line anti-TB injectable drugs, amikacin, kanamycin or capreomycin (WHO, 2010a).

The emergence and spread of drug-resistant TB (MDR and XDR TB) is a major public health concern. Since the incidence of drug-resistant TB is increasing, more and more patients are being exposed to anti-tuberculosis treatment using the less efficacious second-line TB regimens, which are also associated with an increased frequency of adverse effects (WHO, 2008a) and which result in increased frequency of TB drug-induced morbidity and mortality. Other unfortunate consequences of MDR and XDR TB are that the required length of time for treatment is usually prolonged; it has low cure rate of about 60% for MDR-TB (WHO, 2010b), and it is costly both to patients (the cost has been estimated by Tupasi and colleagues at US$ 837 per patient) and to the health system (the cost has been estimated at US$ 3,355 per patient) (Tupasi *et al*., 2006).

The emergence and spread of drug-resistant TB is best prevented by ensuring that only quality-assured TB medicines are prescribed for patients; that patients maintain the required levels of adherence throughout the treatment period, and that the patients themselves and everyone who comes into contact with them observe optimal infection control practices (WHO, 2009b). This study focuses on the patient's experience of those adverse reactions that are associated with second-line TB medicines. The prevention

and control of adverse drug effects necessitates close clinical and laboratory monitoring, adjunctive treatment, specific medical management, hospitalization and skilled nursing care, where necessary. These requirements increase the cost of TB chemotherapy, and the costs associated with them have to be borne by the patients themselves and by the healthcare system. Such procedures and specialized care reduce the personal availability and labor productivity of affected individuals and may thus pose a threat to the economic wellbeing of individuals, their families and of the community as a whole (WHO, 2006a; Tupasi *et al*., 2006).

Risk factors for drug resistant tuberculosis

A number of risk factors have been implicated in the genesis and development of drug-resistant TB. The WHO 2010 Global Report on MDR and XDR-TB surveillance mentions the following key risk factors that are associated with drug-resistant tuberculosis (WHO, 2010b).

1. Irregular use of anti-TB drugs by an individual
2. Behavior associated with males (being an adult male)
3. The existence of HIV infection in a patient prior to TB infection
4. The peculiar susceptibility of young adults (and particularly people between the ages of 15 and 44 years)

Drug resistant tuberculosis in Namibia

In Namibia itself, resistance to available first-line and second-line anti-TB medicines is an extremely serious health hazard that threatens to reverse the gains that have accrued to Namibia as a result of the success that the National Tuberculosis and Leprosy

Program achieved in reducing the burden of TB throughout the country. Table 1 provides a summary of the startling increases in the number of cases of drug-resistant TB that were reported between 2007 and 2009.

Table 1.1: Total reported and confirmed numbers of DR TB cases for the period 2007-2009, Namibia

DRUG RESISTANCE CATEGORY	2007	2008	2009
Number of cases with confirmed MDR-TB (excluding XDR-TB)	116	201	275
Number of cases with confirmed poly-drug-resistant TB	7	47	80
Number of cases with confirmed XDR-TB	3	20	17
Totals	**126**	**268**	**372**

Source: MoHSS, 2010.

Drug resistant tuberculosis (DR-TB) is associated with high morbidity and mortality rates, especially among HIV-infected patients, who may account for more than 50% of TB cases in Namibia. Globally, the rate of MDR-TB in 2007 among new TB cases was 1.6% in contrast to the figure of 8% among previously treated TB cases (WHO, 2009a). In Namibia, it has been observed that drug-resistant tuberculosis affects mostly young and economically productive adults (with a mean age of 35 years), and males in particular (MoHSS, 2010). Almost all these cases of pulmonary tuberculosis are those who have either failed category 1 treatment or who have relapsed after successful treatment with category 1 treatment (MoHSS, 2010). In 2009, the majority of reported DR-TB cases came from six of the following 13 regions of Namibia: Kavango, Khomas, Otjozondjupa, Ohangwena, Oshana and Erongo regions (MoHSS, 2010).

In response to the rapidly growing threat of drug-resistant tuberculosis in Namibia, the Ministry of Health and Social Services, with support from its development and technical partners, is now implementing a program of DR-TB (PMDT) management which has been designed to address and remedy some of the difficulties that have undermined efforts to prevent the emergence and spread of resistance to anti-TB medicines. Some of the interventions in the PMDT program include the ongoing training of health care workers in the effective management of DR-TB, and the establishment of a Central Clinical Review Council (CCRC) for DR-TB, which is charged with the responsibility of reviewing the clinical histories of all DR-TB patients, recommending appropriate treatment regimens for the patients, and providing guidance and technical oversight for the medical management of all MDR-TB patients.

Diagnosis and surveillance of drug-resistant TB in Namibia

The Namibia Institute of Pathology (NIP) provides most of the routine biomedical laboratory testing services needed by state-operated hospitals and primary care health facilities. The NIP has a central reference laboratory in the capital city of Windhoek, where all mycobacterial culture and drug susceptibility testing are undertaken. All testing for resistance to first-line anti-TB drugs is also carried out by NIP, while testing for resistance to second-line anti-TB drugs is performed by the supranational reference TB testing laboratory in South Africa.

While the national surveillance of TB drug-resistance has hitherto been weak, it has significantly improved in the past four years because of the use of an electronic TB register and the surveillance by the central clinical review council (MoHSS, 2010). The implementation of a system for the active surveillance of drug-resistance tuberculosis is

still being developed and the piloting of the e-TB manager tool is being currently undertaken in about six DR-TB treatment facilities in Namibia (Personal communication, Dr. Nununrai Ruswa, NTCP: October 2011).

Challenges in chemotherapy of drug-resistant TB

The treatment of MDR-TB is a complex undertaking that requires long periods of continuous treatment, the combination and administration of 5 - 9 different types of medicines, and strict and conscientious adherence to the requirements of TB chemotherapy. One of the great difficulties is that patients often find it enormously difficult to adhere to these long-term second-line treatment regimens, a problem that is further compounded when they begin to experience intolerable adverse drug reactions (ADRs) (Xu *et al*., 2009). Patient tolerance of the usually mild side-effects of anti-TB drugs is a requirement for achieving complete adherence and successful TB treatment outcomes. Unfortunately, however, severe and serious side-effects, by their very nature, rapidly become intolerable and unacceptable when they jeopardize the lives and quality of life that is experienced by the patient concerned. Adverse drug reactions are therefore implicated in the poor treatment adherence shown by many patients (Zaleski, 2006; MoHSS, 2006; WHO, 2006a; 2007). Fifteen percent (15%) of all patients on MDR-TB chemotherapy described severe adverse reactions as the main reason why they failed to adhere to treatment regimens (Xu *et al*., 2009). In another study, up to 23% of TB patients were compelled to terminate TB chemotherapy during the intensive phase of treatment because of the tremendously adverse effects of the medications (Schaberg *et al*., 1996). As the number of patients being treated for MDR-TB in Namibia increases, the exposure of the TB-infected patient population to the risk of serious ADRs also increases, and this creates an important public health concern because of the increased

risk of TB drug-induced patient harm and its related consequences for the TB control program in Namibia.

TB and HIV co-infection in Namibia

Tuberculosis is one of the most common opportunistic infections observed in patients already infected with HIV, and one of the earliest to appear. HIV associated tuberculosis in Namibia has fluctuated around 58% over the past five years; it was 59% in 2008 and 58% in 2009 (MoHSS, 2010). Drug-resistant tuberculosis is associated with high morbidity and mortality rates among HIV-infected patients, although no data is as yet available to indicate the prevalence of HIV among patients with DR-TB.

Since HIV disease is a serious public health concern in Namibia, it has aggravated the recent TB trends shown in Figure 1.3. Figure 1.3 shows how the rate of TB case notification initially increased and then later began to decline in tandem with the antenatal HIV prevalence trends for the period between 1998 and 2008. (The antenatal prevalence of HIV was measured among women who attended antenatal clinics.)

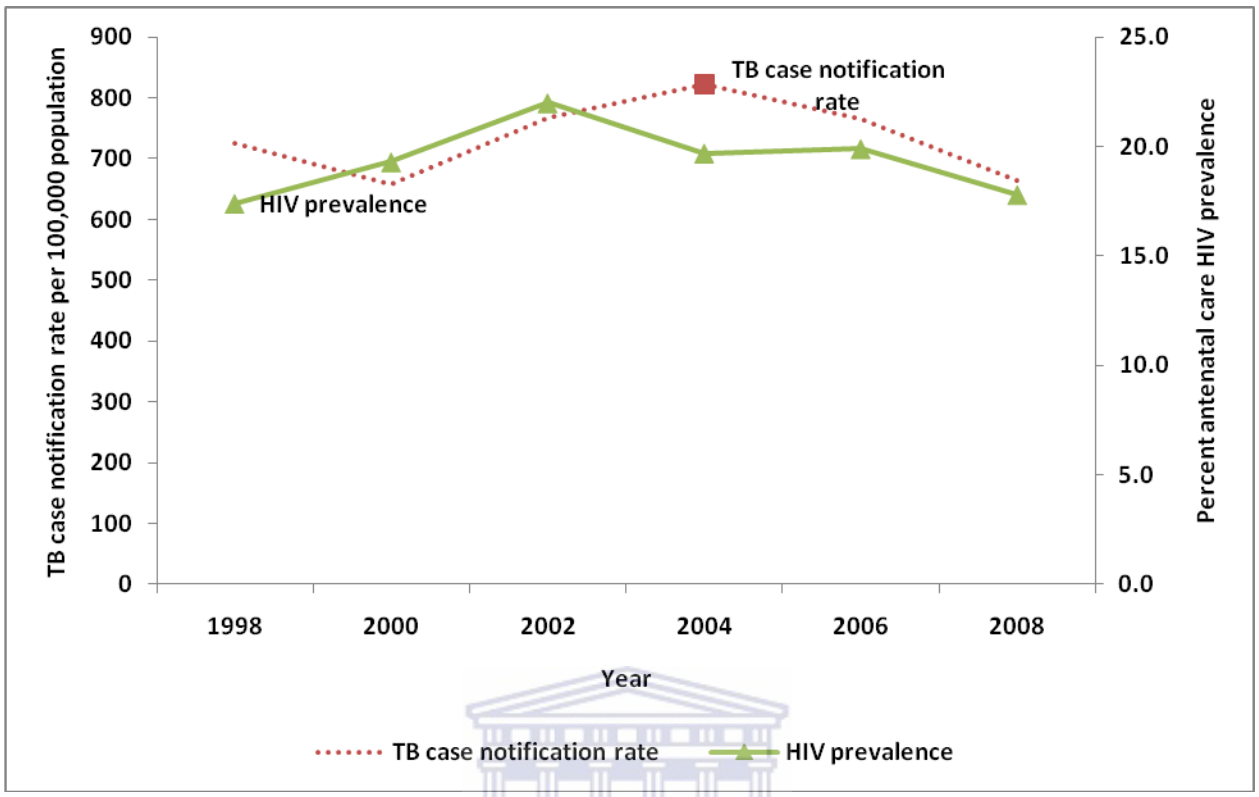


Figure 1.3: Relationship between HIV prevalence and TB case notification rates for the period 1998–2008

Source: MoHSS (2009, 2010)

When studying TB and HIV co-infection in a country with high burdens of both diseases such as Namibia, it is important to understand and be aware of how the various possible combinations of patient sub-groups of co-infection in terms of drug sensitivity and patterns of resistance to *Mycobacterium tuberculosis* and to the human immune deficiency virus in the population, present and show themselves. The matrix in Figure 1.4 (below) shows the four sub-groups that arise, and the relative availability of data about each of the sub-groups of TB/HIV co-infection in Namibia. The figure shows that the majority of affected patients are those with drug-sensitive TB and/or drug-sensitive HIV. These categories are followed by those with drug-resistant TB and drug-sensitive HIV co-infection. This study focuses on patients with drug-resistant TB and

drug-Sensitive HIV co-infection because of the number of DR-TB patients who are co-infected with drug-resistant HIV, is relatively low.

		Type of tuberculosis infection	
		Drug-sensitive TB	**Drug-resistant TB**
HIV infection	**Drug sensitive HIV**	The majority of patients are in this sub-group. Relatively more data is available.	Some data is available
	Drug resistant HIV	Limited amount of data is available.	Limited amount of data is available

Figure 1.4: Four possible sub-groups of patients with TB/ HIV co-infection

Research problem

At the time of conceptualizing and writing the proposal for this study, very little useful documented information about the occurrence, rates and profile of adverse reactions to second-line anti-TB medicines and their predisposing factors in the Namibia's National Tuberculosis Control Programme (NTCP), was available. This lack of information has made it difficult for clinicians to properly manage adverse reactions and optimize TB treatment success in individual patients. It has also made it difficult for TB program managers to effectively plan, design and implement strategies or interventions for

improving the quality of TB treatment and care in TB programs. Doctor D. Panganai expressed a keen interest to document the occurrence of adverse reactions of second-line anti-TB medicines in Namibia (Personal communication, Dr. D. Panganai, TB program manager: February 2009).

This lack of vitally important information indicated the need for local studies that would gather accurate information about the occurrence, rates, characteristics, predictability and possible risk factors of adverse reactions to second-line anti-TB medicines in Namibia.

Study significance

A key challenge faced by clinicians when treating patients with drug-resistant TB in Namibia is their limited ability to predict (for an individual patient) the probability of major adverse effects as a result of a particular second-line anti-TB regimen (or a component drug in the regimen) because of lack of precise local data about patient risk factors for anti-DR-TB medicine-related adverse events. An accurate knowledge of the risk factors associated with particular adverse reactions to medicines will help clinicians and doctors to design interventions to prevent or minimize the future occurrence of adverse effects medicines in patients (Pirmohamed, Breckenridge, Kitteringham and Park, 1998; Riedl and Casillas, 2003). But such knowledge involves a thorough and detailed understanding and evaluation of individual patient adverse drug effect risk factors, as well as an analysis of base-line patient characteristics, contextual and genetic factors. This study was therefore designed to supply the information that was needed about the types, frequency, characteristics and risk-factors associated with adverse

events of drug-resistant anti-TB chemotherapy so that clinicians could make informed choices about the attention, resources and efforts that would be needed for the prevention and clinical management of the serious adverse reactions that are frequently caused by second-line anti-TB medicines, as recommended by Zaleskis (2006).

The setting: A public TB treatment facility in Walvis bay District, Namibia

The research was conducted in a TB treatment facility in the Walvis Bay District of Namibia. Walvis Bay District is located on the Atlantic coast of Namibia. The settlement and its surroundings contain Namibia's main sea port and harbor. Its main economic activity includes port operations and international sea transport, fish processing and tourism. At the time of this study, the Walvis Bay TB treatment facility was serving the second largest number of patients for second-line treatment in Namibia after Katutura Intermediate Hospital (MoHSS, 2006). On average, there are usually 20-25 patients for second-line TB treatment at any one time in the TB ward in this facility. These patients are admitted to the TB ward and are initiated into second-line treatment that takes the form of six months of intensive chemotherapy. Continuation therapy is maintained through a facility-based DOTS-plus program that is run by the health center nearest to the patient. Patients visit the health facility every day between Monday and Friday inclusive for their daily dose of anti-TB medicines.

2. LITERATURE REVIEW

Definitions of key concepts and terms

These definitions and descriptions have been adapted from the following sources: UMC (Uppsala Monitoring Center) (2000); Riedl and Casillas (2003), and WHO (World Health Organization) (2007).

Adverse [drug] reaction (ADR): An adverse [drug] reaction (ADR) is an adverse response to a medicine, which is noxious and unintended and which occurs at doses normally recommended for use in humans.

Side effect: A side effect is any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the drug.

Adverse event or experience: An adverse event or experience is any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship to the treatment.

Unexpected adverse reaction: An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with domestic labeling or marketing authorization, and which is not expected from the characteristics of the drug.

Serious adverse events are those that:

- are life-threatening
- cause or prolong hospital admission
- cause persistent incapacity or disability
- are sometimes caused by misuse or dependence to a particular drug

Avoidable (preventable) adverse reactions: Avoidable adverse reactions are those that can be predicted and that can therefore be prevented from happening.

Seriousness of ADRs: The seriousness of adverse drug reactions is based on the seriousness of the outcome or harm caused to the patient.

Severity of ADR: The severity of an adverse reaction denotes the intensity of the effect, which may be mild, moderate or severe.

Short-term ADR: A short-term ADR occurs within a reasonably short interval after administration (such as minutes or days after the administration of a medicine).

Long-term ADR: A long-term ADR occurs after the passage of a reasonably long period of time (months or years) after the administration of a medicine.

Type A and B adverse effects

Type A adverse effects*:* Type A adverse effects are those that are caused by the heightened (exaggerated) pharmacological effects of a drug. They are fairly common, predictable, dose-related, and are avoided by using doses that are better tolerated by an individual patient.

Type B adverse effects*:* Type B adverse effects are generally rare, unpredictable and may be serious. They may be immunological or non-immunological and occur in patients with often unknown predisposing conditions.

Rare adverse event: A rare adverse event is an event with a probability frequency of between 1 in 10,000 and 1 in 1,000.

Spontaneous reporting system: A spontaneous reporting system is a system whereby case reports of suspected adverse drug events are voluntarily submitted by health professionals, patients and pharmaceutical manufacturers to the national drug regulatory authority.

Classification and coding of ADRs

Adverse reactions may be described and coded in terms of the body's systems and organs by using the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Drug-Resistant TB definitions (MoHSS, 2006)

- **Mono-resistance:** TB that is resistant to a single drug
- **Poly-resistance:** TB that is resistant to more than one drug, but not to the combination of isoniazid and rifampicin
- **Multidrug-resistance (MDR):** TB that is resistant to at least isoniazid and rifampicin
- **Extensively drug-resistance (XDR):** TB that is MDR as well as being resistant to fluoroquinolones and at least one of the three injectable drugs (amikacin, kanamycin, capreomycin)

Principles of the Treatment of Drug-Resistant Tuberculosis

The fourth edition of the World Health Organization guidelines on the treatment of tuberculosis recommends the following principles for the treatment of drug-resistant tuberculosis by national tuberculosis control programs (WHO, 2010a).

According to the guidelines, the aims of the treatment of tuberculosis are to:

- Cure the patient and restore quality of life and productivity
- Prevent death from active TB or its late effects
- Prevent the recurrence of TB and the relapse of the patient
- Reduce the degree of transmission of TB from the patient to others
- Prevent the development and transmission of drug resistance.

These guidelines encourage the regular monitoring of patients in order to facilitate the completion of treatment and to allow the identification and management of any adverse

effects from the anti-TB medicines. In this process, the cohort analysis of TB treatment outcomes is emphasized, especially in patients with drug-resistant tuberculosis.

There are five groups of anti-TB drugs that are recommended for the treatment of MDR-TB. Anti-tuberculosis drugs in Group 1 are the first-line oral agents; Group 2 are injectable agents; Group 3 are fluoroquinolones; Group 4 are oral bacteriostatic second-line agents, and Group 5 are agents with an as-yet unclear role in the treatment of TB. In composing a regimen for treating drug-resistant tuberculosis, the following basic principles must be adhered to:

- Use any first-line drug that is likely to be effective (Group1).
- Include aminoglycoside or capreomycin (Group 2).
- A fluoroquinolone should always be used if deemed likely to be effective (Group 3).
- Use the remaining Group 4 drugs to make a regimen of at least four effective agents.
- Use Group 5 drugs as needed to make a regimen of at least four effective agents.
- The initial phase of second-line therapy occurs in a referral hospital.
- All doses of second-line therapy must be directly observed for the entire duration of therapy.
    - Use a community-based DOT approach where possible.
- Second-line therapy is given for all seven days per week, but the injectable drug need only be given for six days per week, with one day of rest (for example. on Sunday).

The Namibia Ministry of Health and Social Services (National Tuberculosis and Leprosy Control Programme) has adopted an individualized DR-TB treatment

approach. In terms of this approach, patient regimens are custom-made, and are based on the drug susceptibility testing (DST) of first-line and additional second-line drugs (MoHSS, 2006). The recommended second-line anti-TB medicines for the intensive and continuation phases of MDR-TB treatment are shown in Table 2.1. The combination of several drugs prevents the further development of resistance because it avoids the selection of naturally resistant mutants.Because of widespread concerns about the loss of efficacy due to patient resistance to ciprofloxacin and the emergence of a higher rate of serious adverse effects caused by amikacin, these two drugs were removed by Namibia's Ministry of Health and Social Services from the list of recommended drugs in 2008.

Table 2.1: Recommended second-line anti-TB medicines in Namibia

Initial Phase		Continuation Phase	
Medicines	Duration in months of administration	Medicines	Duration in months of administration
Kanamycin Ethionamide Cycloserine Levofloxacin Pyrazinamide +/-Ethambutol Pyridoxine	At least 6 months and 4 months post-culture conversion	Ethionamide Levofloxacin Cycloserine	At least 18 months

(*Source: MoHSS, 2006:74*)

Prevalence of adverse effects of second-line anti-TB medicines

Various studies have reported a high frequency of the occurrence (43-95%) of at least one adverse reaction, of any type and characteristic, to anti-TB medicines (Nahar *et al*., 2006 [N=64]; Yee *et al*., 2003 [N=430]; Furin *et al*., 2001 [N=60]; Chhetri *et al*., 2008 [N=137]; Kishore *et al*, 2008 [N=326]; and Gholami *et al*., 2006 [N=83]). In general, second-line anti-TB regimens have been described as having a higher prevalence of adverse effects (up to 95%), when compared to first-line regimens, where the prevalence of adverse effects was 50% in the study by Nahar *et al*., (2006).

One study in a TB treatment facility in Iran described the most frequently reported adverse reactions among patients on anti-TB medicines to have been those that involve the hepatobiliary system (37%) and the gastro-intestinal system (21%), (Gholami *et al*., 2006). In addition to this, most (i.e. about 50%) of adverse reactions to anti-TB medicines have been graded as mild, (Kishore *et al*., 2008), while serious adverse reactions were reported to appear in between 2.5% and 11% of patients (Gholami*et et al*., 2006; Koshore *et al*., 2008).

Assessing causality of adverse effects to second-line anti-tuberculosis medicines

The assessment of the causality of adverse effects to second-line anti-tuberculosis medicines is complicated by the number of medicines that are involved in the intensive phase and the continuation phase regimens. In addition to this, some of the adverse effects may be common to a number of medicines, and this makes it difficult to attribute particular adverse effects to a specific drug. In addition, the use of fixed dose combinations may make it difficult to perform a pharmacological challenge-re-challenge test for a suspected drug.

While the clinical assessment of the causality of a specific adverse drug reaction in individual patients may be assessed by making use of the Naranjo algorithm, the WHO criteria or any other method, an epidemiologic study is required to investigate risk-factors at in the population at large (Strom, 2005). The Naranjo algorithm consists of 9 questions and related scores (Table 2.2). After a researcher has obtained answers to all of the nine questions and allocated the score appropriate to the question, it is possible to calculate the total score and the probability of an adverse reaction occurring by making use of the following scale:

Definite > 9 *Probable* 5–8 *Possible* 1–4 *Doubtful* 0

Table 2.2: The Naranjo algorithm

Question	Yes	No	Do Not Know
1. Are there previous conclusive reports about this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or when a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5. Are there any possible alternate causes (other than the drug) that could have caused the reaction?	-1	+2	0
6. Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
7. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
8. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
9. Was the adverse event confirmed by objective evidence?	+1	0	0

Source: Naranjo, Busto, Sellers et al. (1981)

The risk and burden of adverse events associated with second-line anti-TB medicines

It is important to monitor any adverse events that might be associated with the treatment of drug-resistant tuberculosis because of the potential impact they may have on the treatment and its outcomes. According to the American Society of Health System Pharmacists Technical Bulletins (1995), severe or serious adverse effects of medicines may:

- Require the discontinuation of the use of the offending drug
- Require the choice of another drug that will have the same therapeutic value
- Require modification of the dose
- Require a patient to be admitted to a hospital
- Prolong the stay of a patient in a health care facility
- Necessitate supportive treatment
- Significantly complicated the diagnosis
- Negatively affect patient prognosis
- Result in temporary or permanent harm, disability, or death

Such severe or serious adverse effects may be experienced by patients treated for drug-resistant tuberculosis using second-line anti-TB medicines.

Medicines that are used in the treatment of drug-resistant *Mycobacterium tuberculosis*, when compared with those that are used for first-line regimens, are far more likely to elicit adverse reactions in the patients who are receiving them (Perri and Bonora, 2004; Zaleskis, 2006). The use of these medicines requires prolonged treatment, close monitoring, and the prevention or minimization of the possible adverse side effects (MoHSS, 2006; WHO, 2008b). It should be borne in mind that the adverse reactions

suffered by patients because of the anti-TB medicines that are used in the TB public health treatment program, can be a significant cause of morbidity and mortality. These factors pose a significant threat to the credibility and success of the program itself (WHO, 2006). The frequencies of various adverse events associated with anti-TB medicines have been widely identified and described in the relevant literature, and they include: abdominal pain (7-30%), nausea and vomiting (5-10%), gastritis (1.7-100%), joint pain (6-35%), visual disturbances (0.7-40%), skin reactions (0-43%), hearing loss (6%), renal toxicity (3.3-4.7%), hepatotoxicity (1.7-57%), peripheral neuropathy (4.7-16%) and psychotic disorders (10%), (Nahar *et al*., 2006; Yee *et al*., 2003; Furin *et al*., 2001; Chhetri *et al*., 2008; Kishore *et al*., 2008; Gholami *et al*., 2009).

As has already been noted above, the adverse effects that a patient suffers because of anti-TB medicines can hamper that patient's adherence to the necessary TB treatment schedules, and so increase the resistance of *Mycobacteria tuberculosis* and promote a relapse of TB disease (Zaleski, 2006; WHO, 2006; 2007). In their study, Fernandez-Villar *et al*. (2004) reported that moderate to severe hepatotoxicity was caused by anti-TB medicines, and that this accounted for 5.5% of the modification or suspension of the initial TB treatment regimens, while about 2% of patients had their regimens suspended because of other serious adverse drug reactions. It is possible for each medicine that is used in the treatment of MDR-TB to elicit serious adverse drug reactions with varying degrees of severity and frequency, and this can make it necessary to withdraw the drug permanently from the regimen. Figure 4, which was constructed from data obtained by from Cox and colleagues, illustrates this same point (Cox, Kalon, Allamuratova, Sizaire, Tigay, Sabine *et al*., 2007).

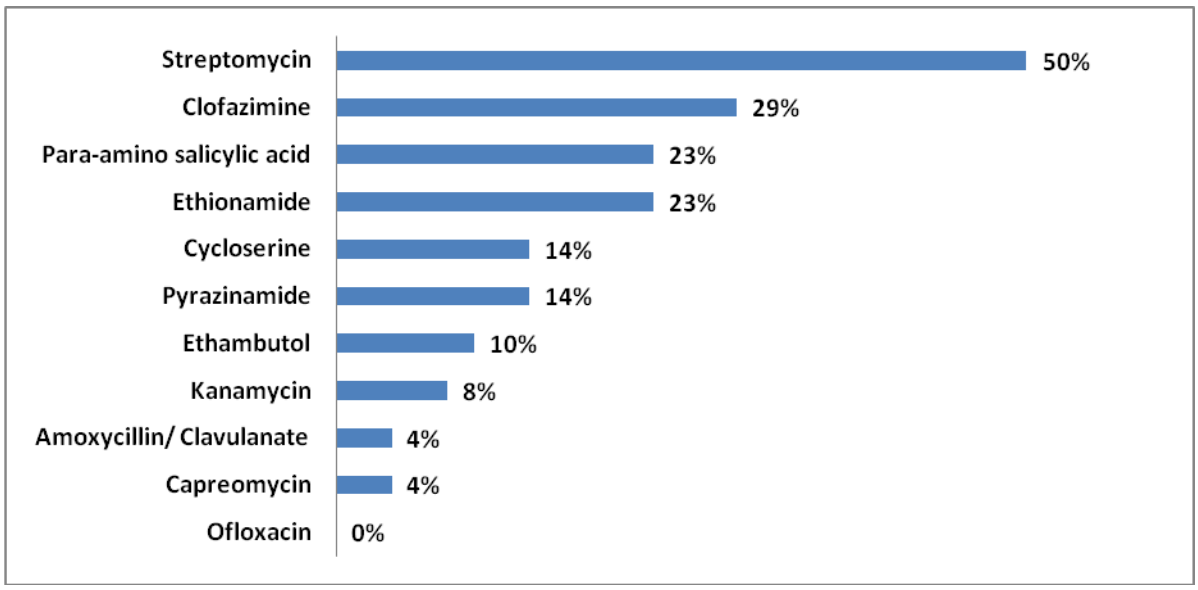


Figure 2.1: Percentage of cases in which second-line anti-TB medicines were discontinued because of serious adverse drug reactions on the part of patients

Source: Cox et al., 2007

Risk factors for adverse events associated with second-line anti-tuberculosis medicines

Various patient-related factors have been reported to be associated with an increased risk of experiencing an adverse reaction to TB chemotherapy. Yee *et al*., (2003), using a prospective cohort design, coupled with detailed review of cases in whom ADRs occurred, studied the major adverse effects of first-line anti-TB treatment in a TB treatment program in Canada. They reported a low incidence (1.48 ADRs per patient-month of follow-up) of major ADRs to the conventional first line anti-TB medicines. By using multivariate regression analysis (cox proportional hazards), these investigators found that the occurrence of any major adverse effects was associated with being female (adjusted hazard ratio 2.5; 95% CI 1.3- 4.7); to being over 60 years of age (adjusted hazard ratio 2.9; 95% CI 1.3- 6.3); to being of Asian descent (adjusted hazard ratio 2.5;

95% CI 1.3- 5.0), and to having an HIV-positive status (adjusted hazard ratio 3.8; 95% CI 1.05- 13.4).

The literature review by Riedl and Casillas, (2003) and the case-control study by Pande, Singh, Khilnani and Tandon, (1996), both highlighted the role of other potential risk factors. These include the habitual consumption of alcohol, co-morbidities, concurrent medications, the duration of TB treatment, and the patient's weight. In a prospective study of 50 patients conducted in Nepal by Shakya, Rao and Shrestha (2004), female gender, disease extent and poor nutritional status were reported as the most important predisposing factors for the hepatotoxicity caused by anti-TB medicines. In addition, Pande, *et al*. (1996) included slow acetylator status as a potential risk factor for isoniazid toxicity. Similar risks factors were identified in studies by Nahar *et al*., (2006); Furin *et al*., (2001); Chhetri *et al*., (2008); Kishore *et al*., (2008); Gholami *et al*., (2009); Mehta *et al*., (2007) and Pirmohamed *et al*., (1998). Riedl and Casillas (2003), however, whose systematic literature review concentrated on adverse reactions of an immunologic nature (Type B ADRs), included previous hypersensitivity to related drugs as an additional factor. It is instructive to note that these studies focused on either first-line or second-line anti-TB medicines (or both regimes) in different demographic, geographic, social, cultural and practice settings. This variability in study parameters should be considered in the interpretation and comparison of these studies.

In addition to the observational cohort and case-control study designs that have been commonly employed in studying adverse reactions of anti-TB medicines in clinical practice settings; other methods have also been applied in studying risk factors for the ADRs. This includes the nested case-control design applied by Chang, Leung, Yew and Tam (2007) and Okwera *et al.* (1997).

The literature review has highlighted limited published research on risk factors associated with adverse reactions to second-line anti-tuberculosis treatment in sub-Sahara Africa, particularly in Namibia. Basing on the above literature review, the main factors that could predict the risk of experiencing an adverse reaction to second-line TB chemotherapy include: advanced age, female gender, racial/ethnic background, extent of the disease, nutritional status, co-morbidities, concurrent medications, the duration of anti-TB treatment, pharmacogenetic factors, and patient's weight.

Concurrent treatment of DR-TB and HIV co-infection

HIV-associated TB infection is common in Namibia (MoHSS, 2010). The concurrent treatment of TB and HIV is known to be beneficial because it is associated with low rates of patient morbidity and mortality (Hafkin, Gammino and Amon, 2010).

Co-trimoxazole prophylaxis is indicated for HIV-infected patients who are not yet on antiretroviral treatment (ART). Isoniazid prophylaxis, on the other hand, is indicated for HIV-infected patients without active tuberculosis disease (MoHSS, 2006; WHO, 2010a).

The co-treatment of TB and HIV by making use of anti-TB and antiretroviral medicines is often challenging for both patients and clinicians. This is caused by an increased patient pill burden, overlapping adverse reactions, drug-drug interactions, and the immune reconstitution syndrome (IRIS). The concurrent treatment of HIV and DR-TB may involve a combined pill burden of 9-10 drugs in the intensive phase of treatment and 6-7 drugs during the continuation phase (Venkatesh, Swaminathan, Andrews and Mayer, 2011). Such a high pill burden may negatively impact patient adherence to the treatment regimen. But the use of fixed-dose combinations of anti-TB and antiretroviral

medicines can substantially reduce the patients' pill burden and hence promote adherence to treatment.

Overlapping adverse effects and drug-drug interactions are common occurrences in the concomitant treatment of drug-resistant TB and HIV infection. Thus, for example, while gastrointestinal intolerance is frequently encountered with the use of zidovudine, protease inhibitors, para-aminosalicylic acid and ethionamide, neuropsychiatric adverse events are common with the use of efavirenz and cycloserine (Hafkin, Gammino and Amon, 2010; WHO, 2010a).

Since didanosine formulations contain an antacid that binds to fluoroquinolones, this prevents their absorption and hence reduces their intended efficacy and effectiveness. In a similar way, clarithromycin decreases the absorption of zidovudine while nevirapine and efavirenz decrease the plasma levels of clarithromycin (Hafkin, Gammino and Amon, 2010).

Immune reconstitution syndrome (IRIS) refers to a transient worsening of symptoms and signs of tuberculosis disease or radiographic deterioration soon after the initiation of antiretroviral therapy, despite reductions in the plasma viral load and evidence of immunological recovery (Venkatesh, Swaminathan, Andrews and Mayer, 2011). Such a paradoxical response to treatment may be a source of confusion to a clinician who is treating a patient with DR-TB who is simultaneously co-infected with HIV and may be erroneously misinterpreted by the clinician to be an adverse reaction to anti-TB medication.

In addition to the clinical challenge posed by IRIS, the diagnosis of tuberculosis infection by making use of smear microscopy is usually difficult in people living with HIV (MoHSS, 2006). The diagnosis of HIV-associated tuberculosis (and therefore, DR-TB) , therefore, requires the use of other, more sensitive diagnostic methods.

Conceptual framework for studying adverse effects of second-line anti-TB medicines

The key factors to consider while quantifying the magnitude of risk of individual adverse events and when investigating the risk factors for those events are summarized in the conceptual framework in Figure 2.2 below:

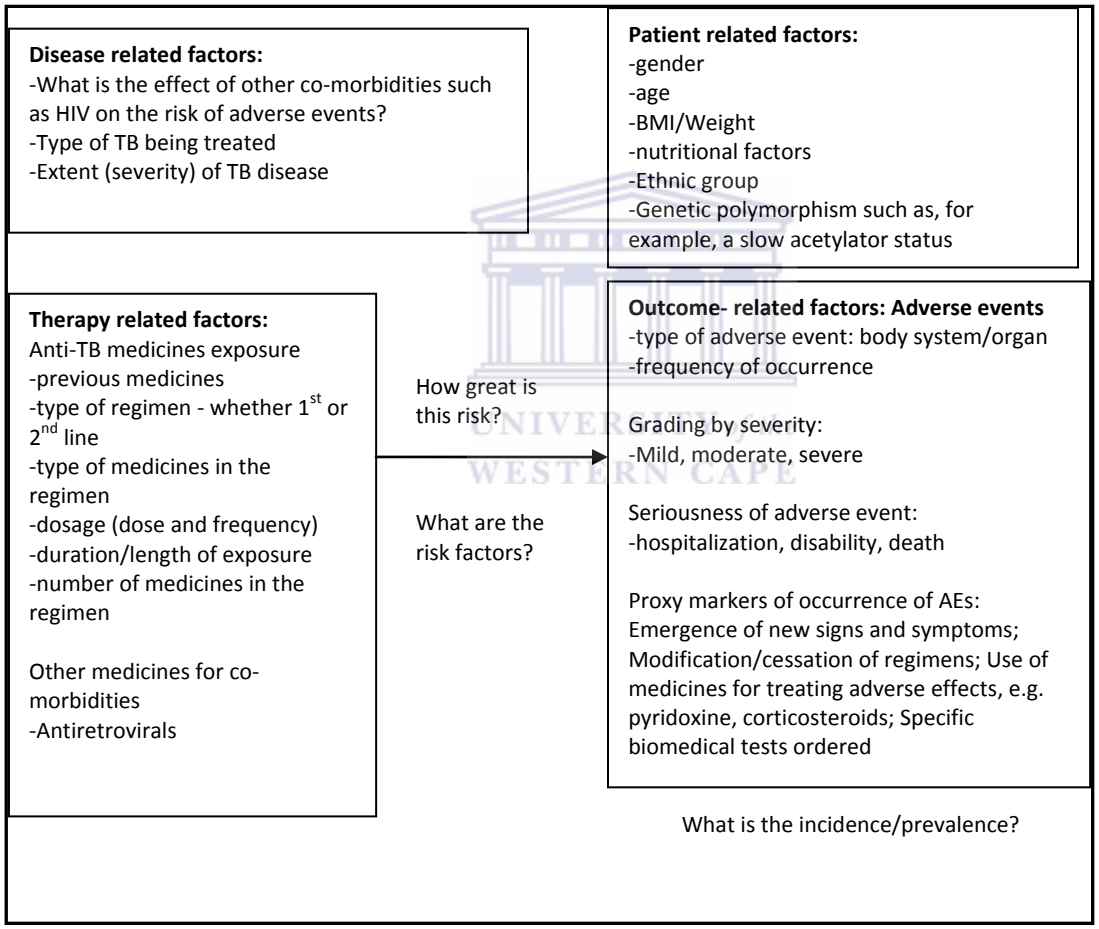


Figure 2.2: Conceptual framework for studying the adverse effects of anti-TB medicines

Prevention and management of adverse effects of second-line anti-tuberculosis medicines

Although second-line anti-tuberculosis drugs have many more adverse effects than first-line anti-TB drugs, the successful prevention and management of these adverse effects is possible, even in resource-limited settings such as those in Namibia (WHO, 2010a). There are several strategies that could be used in the prevention and clinical management of adverse effects of second-line anti-tuberculosis medicines. According to the WHO guidelines for the treatment of tuberculosis (WHO, 2010a), patients should be screened for the side-effects of medication at every DOTS/ DOTS-plus encounter with the treating clinician. It is also important that patients should be educated about the possible adverse-effects of their anti-TB medications. They should have access to clinical and laboratory services to help detect adverse-effects, and they should have access to medications to treat adverse effects when they occur.

It is important clinically to particularly monitor patients during the intensive phase of treatment of DR-TB so that adverse effects can be promptly detected and properly managed. Routine laboratory monitoring is not necessary, according to the World Health Organization (WHO, 2010a). Namibia's National Tuberculosis and Leprosy Control Program and the Therapeutics Information and Pharmacovigilance Center (TIPC) encourage health personnel to monitor adverse effects of DR-TB medicines by teaching health personnel and patients how to recognize and manage the symptoms of common adverse effects, and by urging them to report and document such symptoms when they occur. Patients are also asked about any such symptoms when they come to collect their anti-TB drugs. Adverse events are recorded on the MDR-TB drug side effect monitoring form (Appendix 6).

Symptom-based approach to managing adverse-effects of anti-TB drugs

The World Health Organization and National TB Treatment Guidelines recommend that adverse effects should be classified as either minor or major (WHO, 2010a and MoHSS, 2006). In general, according to these two guidelines, a patient who develops minor adverse effects should continue to receive treatment for TB treatment and should be given symptomatic (adjunctive or palliative) treatment for the minor adverse side effects. If a patient develops a major adverse effect, the treatment or responsible (suspected) drug should be discontinued, and the patient should be urgently referred to a clinician or health care facility for further assessment and treatment. All patients who experience major adverse reactions to medications should be managed in a hospital.

Zaleskis (2006) recommends the following actions if symptoms of adverse effects occur:

- Check and verify the dose of the suspected drug.
- Exclude all other possible causes of the symptom.
- Determine the seriousness and extent of the adverse effect.
- Record and document the adverse effect.
- Gradually re-introduce the suspected drug when the symptoms have disappeared.
- Avoid the possibility of creating resistance to the drug concerned.

Clinicians and other health personnel should be encouraged to apply the above principles so that they will be in a position to minimize the occurrence of unpleasant side effects and mitigate adverse reactions of DR-TB medicines. In doing so, patient adherence to second-line anti-tuberculosis treatment, and the success of the chemotherapy of drug-resistant tuberculosis, may be greatly improved.

3. AIM AND OBJECTIVES

Aim

The aim of the study was to measure the occurrence of adverse events in adults with drug-resistant tuberculosis being managed with second-line TB therapy and investigate the association between risk factors and adverse events in a district in Namibia.

Objectives

The objectives of this study were to:

1. Determine the types and frequency of adverse events that occur during the treatment of drug-resistant tuberculosis in a sample of patients at the selected TB treatment district facility in Namibia
2. Describe the characteristics, duration and outcomes of the adverse events with special reference to HIV-positive and HIV-negative patients
3. Identify risk factors that are associated with the occurrence of adverse events to second-line anti-TB medicines, and examine the influence of HIV infection and antiretroviral therapy
4. Make policy recommendations for the National Tuberculosis Control Programme (NTCP)

4. METHODOLOGY

Study design

The researcher used an observational, cross-sectional, descriptive and analytic study design to determine the prevalence of the adverse events of second-line anti-TB medicines and to analyze their associated risk factors. The chosen design required the researcher to review the patients' TB treatment records. The descriptive aspect relied on an analysis of the quantification of the prevalence (relative frequency) and distribution of adverse events to drug-resistant tuberculosis treatment that occurred in the study sample. The analytic component compared patient sub-groups and variables in order to identify risk factors and to characterize the nature of the association between risk factors and the occurrence of the adverse effects caused by anti-tuberculosis medicines. Since this was a cross-sectional study, treatment exposure, baseline factors and outcomes of interest were all measured at the same point in time. The study therefore generated information about the prevalence of the adverse events that occurred during the treatment of drug-resistant tuberculosis (Beaglehole, Bonita and Kjellstrom, 1993; Enarson, Kennedy, Miller and Bakke, 2001).

Selection of study facility: The researcher purposively selected this TB treatment facility for the study because of its relatively good DR-TB treatment adverse event data documentation practices at the facility during the time period covered by the study (Personal communication, Dr. Nunurai Ruswa, NTCP: July, 2009).

Adverse events at the facility are monitored daily by the clinical staff treating the patient, and these are recorded on a standard MDR-TB drug side effect monitoring form that has been standardized by the Ministry of Health and Social Services. There is a

separate form for monitoring and recording whatever adverse events might occur in the intensive and continuation phase of DR-TB treatment (Appendix 6).

Study population: The study population included all the patients who were treated with second-line anti-TB medicines at a specific TB treatment facility in Namibia between 01 January 2008 and 24 February 2010, both dates being inclusive.

There were only 59 adults with drug-resistant tuberculosis in the selected facility during the study period. All the 59 records were used in the study sample and were examined in order to determine the occurrence of adverse events during second-line TB treatment and the associated risk factors associated. However, the following sample size calculations have been provided to illustrate what the sample size would have been had there been sufficient numbers of patients.

Sample selection

The selected sample included all patients who satisfied the study's inclusion and exclusion criteria. All patients who had been treated with second-line anti-TB medicines at the study facility between 01 January 2008 and 24 February 2010 were included. Patients with missing records or those with missing data on exposure or outcome variables were excluded.

Given that there were only 59 records for the number of TB patients treated with second-line TB medicines at the selected TB ward from 01 January 2008 to the day of data collection, the researcher decided to include all the patients whose treatment records were available on the day of data collection, and whose records corresponded

to the defined study period. No sampling was conducted because the available patient numbers were fewer than that required for the calculated sample size.

Data collection

Data were collected retrospectively. Similar retrospective (records review) data collection methods have been successfully employed by Furin *et al*., (2001) and Torun *et al*., (2005) in their study of the adverse effects of second-line anti-TB medicines, and these have included risk-factor analyses.

The researcher made use of a structured data collection form to extract the required data during the review of each patient's TB treatment records. Such a form was necessary because the record's review process was retrospective and focused on the patient's documents rather than on the patients themselves. A sample of the data collection form and coding scheme is found in Appendix 1. Data was collected on the following study variables as a result of a review of each patient's medical and TB treatment records:

Independent variables: Age, Gender, Initial patient weight in kilograms, Mother tongue, Date TB treatment commenced, Type of TB, Duration of the intensive phase, continuation phase and total phase of TB treatment, Treatment regimen, Number of medicines in the regimen, Stage of treatment, Concomitant medications, Co-morbidities and the Time to the onset of the main adverse event.

Dependent (outcome) variable: Occurrence of adverse event (Yes or No).

Characterization of the dependent variable (adverse events): This entailed the further description of the adverse event(s) such as, for example, rash on the skin, the grading of the seriousness of adverse events, the duration of adverse events, actions taken to manage the adverse events, and the outcomes of the adverse events.

Data analysis

The researcher coded the data by using the basic scheme depicted on the data collection form in Appendix 1. The coded data was then single-entered into Epi Info, version 3.4.3 (November 2007) for data management and statistical analysis. There being few records and manageable records (59), the researcher went through all data entered into the statistical software and verified the accuracy and completeness of data entry against the manual data collection forms. Any errors and discrepancies were investigated and rectified. Microsoft Excel® (2010) was then used to draw the charts. This approach is similar to that employed by Furin and colleagues (Furin *et al*., 2001) used Microsoft Excel for data entry and Epi Info 6.0 for statistical analysis in their study of the occurrence of serious adverse effects in patients receiving therapy for multi-drug resistant tuberculosis. Categorical data was coded either as mutually exclusive choices or multiple response choices or short descriptive text to facilitate computerized analysis. Continuous numerical data such as patient age and initial body weight were entered as numeric variables. The data was cleaned through visual checks on raw data set and by exploratory graphical analysis of the frequency distributions of the data in order to identify and correct any erroneous, strange, unusual or outlier values.

Both descriptive and analytic statistical methods were performed on the collected data. Descriptive statistics were used to describe the frequencies and distributions of the

various variables studied. These were also used to determine the prevalence of the reported adverse effects of the second-line anti-TB chemotherapy. Measures of central tendency and dispersion such as mean and standard deviation (mean ± SD), and median and inter quartile range (IQR), were used to summarize and describe the data set for quantitative variables. The non-paired Student's t-test for univariate analysis was used to compare the means of continuous variables, such as age, between two sub-groups, such as gender. As recommended by Katzenellenbogen, Joubert and Abdool Karim, (1997), exploratory methods were first utilized to obtain a general picture of the information contained in the data set, including an impression of the type of frequency distribution of the data variables, before proceeding with the detailed analysis.

Subsequently, statistical methods of examining associations between variables were used to analyze the nature and strength of associations between various risk factors and the occurrence of adverse events related to the administration of second-line anti-TB medicines to patients in the study sample.

A series of cross-tabulations for the bivariate analysis of a potential risk factor and the occurrence of grouped or single adverse event were constructed. The researcher calculated the relative risks and/ or odds ratios from the contingency tables and the chi-square statistic (χ^2) or Fisher's exact test. He also made use of the logistic regression models to calculate the Odds ratios for multiple risk factors, and used confidence intervals (95%) and p-values ($p< 0.05$) to determine the statistical significance of the calculated risk ratios. A similarly designed study by Mendes, Cordeiro and Burdmann, (2009) that assessed the prevalence and risk-factors for acute kidney injury in patients with polymyxin B, applied the chi-square statistic (χ^2) or Fisher's exact test and the non-paired Student's t-test for univariate analysis to compare the means of continuous variables. These investigators applied binary logistic regression for the analysis of risk-

factors, since this regression model allows for the simultaneous analysis of more than one risk factor or independent variable. In this study, the researcher applied multivariate logistic regression analysis to examine the effect of multiple risk factors on the adverse event outcome of interest.

Validity and bias

Selection bias: Since all of the patients who were receiving treatment at the TB treatment facility during the study period were included in the sample, there was minimal risk of selection bias. No systematic differences in the selection or follow-up of patient records were observed by the researcher.

Information bias: The facility TB treatment register and clinical records may have been completed with varying degrees of thoroughness and accuracy because of variations in clinician's conscientiousness and attention to detail. This phenomenon was considered by the researcher to be random in nature, hence may have led to non-differential information bias, which may have biased the risk estimates towards the null. The risk of information bias was therefore non-differential because the variation in the level of completion of patient treatment records was not related to the prior knowledge of the attending clinician with regard to specific drug exposures or the occurrence of specific adverse event(s).

Because the varying lengths of time for which each patient had been receiving anti-TB treatment when the data was collected, there could have been a differential bias between patient exposure to specific anti-TB drugs and the risk of adverse events, which may have biased the risk estimates either towards or away from the null. This

bias was adjusted for during multivariate analysis using length of time on treatment as a confounder.

Lastly, the researcher performed no causality analysis on patient-reported adverse events, which could have served to introduce a misclassification bias as to whether the adverse event was due to a specific drug or not.

Confounding: The researcher used stratification and multivariate analyses in the analysis stage to control for the measured, potential confounders.

Stratification

The following variables were used for stratification: HIV status, ARV use status, gender, diagnostic category of DR-TB (mono/poly drug-resistant TB; multi (extensively) drug-resistant TB, prescription (use) of selected anti-TB medicines (such as, cycloserine), and the stage of treatment (intensive versus continuation phase).

Multivariate analysis

The researcher used more than one covariate during multivariate analysis to examine the effect of the introduction of other variables into the estimated risk measure (Odds ratio). For example, in analyzing the risk of joint pain caused by the use of cycloserine-containing anti-TB regimens, the researcher applied a multivariable model that included age ≥45 years, female gender, the use of cycloserine, the use of kanamycin, the use of levofloxacin, HIV status, and a baseline body weight ≤ 45 kilograms.

Precision and Reliability: The same data collector and data collection tool was used to collect the required data so that variations in data would be minimized. It was, however, challenging for the researcher to determine the precise time when a particular adverse event had occurred.

5. ETHICAL CONSIDERATIONS

This retrospective study involved the review of medical records of patients who were currently on treatment for drug-resistant tuberculosis, or those who had completed their treatment for drug-resistant tuberculosis. But since there was no direct interaction between the researcher and patients, there was no direct risk to the study subjects that arose because of the conduct of this study. The researcher abided by the following ethical principles during the design, the requests for the relevant approvals and during the conduct of the study:

Anonymity: Specific patient identifiers were omitted from the study data set in order to guarantee the privacy of the individuals from whom the data was collected. In addition to this, the data was reported in a de-identified and an aggregate manner.

Confidentiality: The researcher observed the utmost confidentiality during the conduct of the study. He protected the study data files from unauthorized access by using a password to gain controlled access, and locked raw data forms securely in a cupboard. The key to this cupboard was always kept by the researcher and by the researcher alone.

Ethical clearance: Ethical approval for the study was obtained from the University of the Western Cape (UWC) Higher Degrees Committee, as well as from the Ministry of Health and Social Services (MoHSS) research unit (Appendix 2 and 3).

Study approval: The researcher sought permission to conduct this study from the Permanent Secretary, Ministry of Health and Social Services, Namibia (Appendix 3).

Permission to collect data from the facility: The researcher sought formal permission to collect data from the patients' treatment records at the study facility from the facility management by means of a letter addressed to the Principal Medical officer (Appendix 4 and 5).

6. RESULTS

Descriptive analysis

The flow diagram below summarizes the distribution of the 59 patients included in the study, according to their HIV status and antiretroviral treatment.

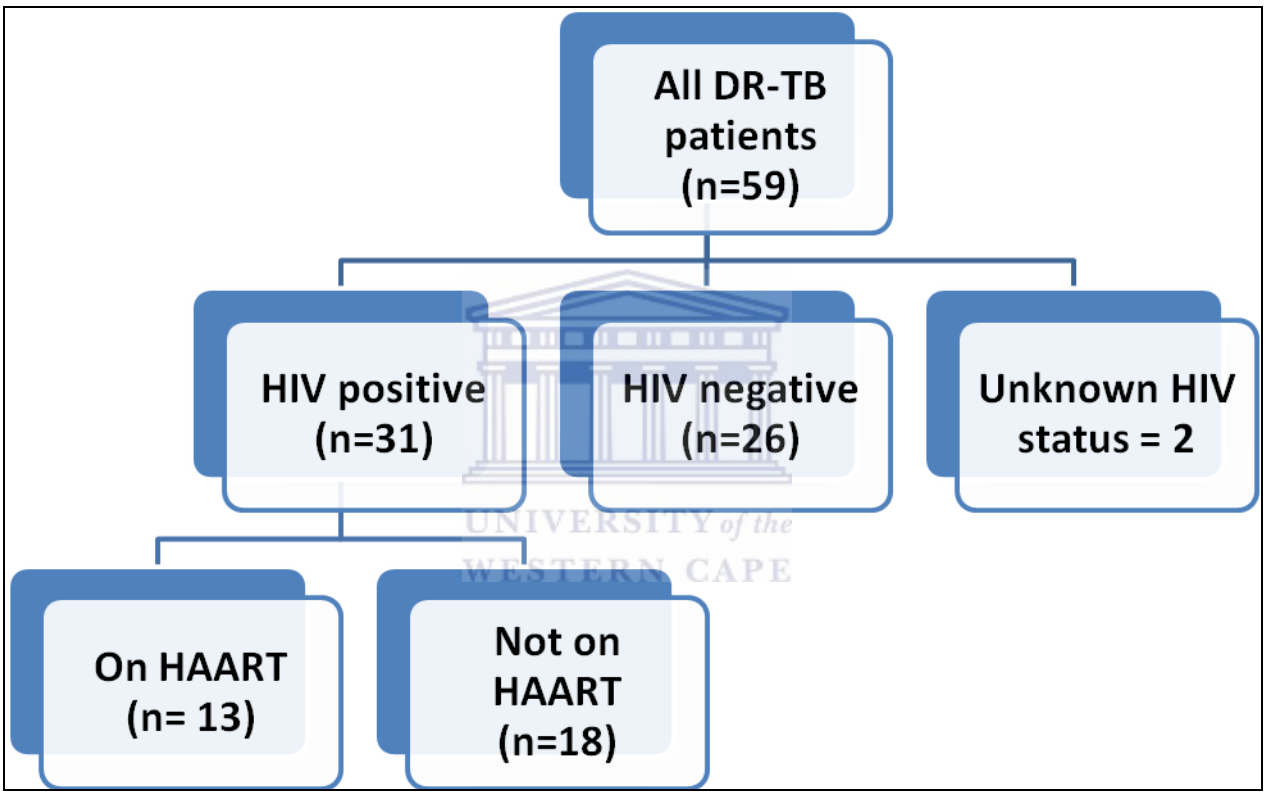


Figure 6.1: Distribution of patients with drug-resistant tuberculosis, based on their HIV status and antiretroviral treatment (N=59)

Fifty-nine patients were treated for DR-TB during the study period. There were more males (66%) than females in the sample. The mean age of the patients was 34.7 years (Table 4). The males in the sample were slightly older than the females (36.9 as against 31 years respectively; p = 0.02). The mean baseline weight was 52.5 kilograms, with no

statistically significant gender difference (53.6 kgs-males, 49.8 kgs-females; p=0.23). About one-third of the patients were unemployed.

Table 6.1: Some demographic characteristics of adults treated for DR-TB at the study site, 2008-2010

Characteristic	n (%) N=59
Gender	
Male	38 (64%)
Female	20 (34%)
Missing	1 (2%)
Age (years) ± SD; median (IQR)	34.7 ± 9.4; 34 (27-42)
Male	36.9 ± 8.4; 37.5 (31-42)
Female	31.0 ± 10.2; 31 (24.5-37.5)
Weight (kgs) ± SD; median (IQR)	52.5 ± 11.3; 52.3 (47-60)
Male	53.6 ± 7.8; 54 (49.3-59.6)
Female	49.8 ± 16.4; 45.6 (40.8-54.6)
Occupation	
Unemployed	18 (31%)
Employed	20 (34%)
Student	1 (2%)
Missing	20 (34%)

SD = standard deviation; kgs = kilograms; IQR = interquartile range

Table 6.2 shows that almost all (92%) the patients had a prior history of treatment with either first-line or second-line anti-tuberculosis medicines. Over three quarters (78%) of the 59 patients had been previously treated with first-line anti-tuberculosis medicines including isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin.

Table 6.2: Clinical characteristics of the 59 patients treated for DR-TB at the study site, 2008-2010

Characteristic	n (%)
Type of TB	
PTB smear +	55 (93%)
PTB smear -	3 (5%)
EPTB	1 (2%)
Diagnostic category of DR-TB	
Previously treated with 1st line medicines	46 (78%)
Previously treated with 2nd line medicines	8 (14%)
New patient, never treated for TB	5 (8%)
TB drug-resistance pattern	
MDR	36 (61%)
Poly-resistant	18 (28%)
XDR	1 (2%)
Missing	4 (6%)

TB = tuberculosis; PTB = pulmonary tuberculosis; + = positive; - = negative; EPTB = extra pulmonary tuberculosis; DR-TB = drug-resistant TB; MDR = multidrug-resistant; XDR = extensively drug-resistant

Table 6.3 shows that approximately half of the patients (31/59 or 53%) were co-infected with the human immunodeficiency virus (HIV). Of the 31 HIV co-infected DR-TB patients, 13 (42%) were being treated with highly active antiretroviral treatment (HAART).

The MoHSS ART guidelines applied during the period covered by this study required the CD4 cell counts of less than 200 cells per cubic millimeter (cells/mm^3) as part of the eligibility criteria for patients to be started on treatment (ART). Not all of the HIV-

positive TB patients were therefore eligible for ART. This explains why the other 18 out of the 31 HIV-infected patients (58%) were not on ARVs.

While all of the patients receiving anti-tuberculosis treatment were also receiving adjunctive pyridoxine treatment, all of the patients with an HIV-positive diagnosis were on cotrimoxazole prophylaxis treatment.

Table 6.3: Treatment characteristics of the 59 patients treated for drug-resistant tuberculosis

Characteristic	n (%)
Number of medicines in anti-TB regimen; median (range)	
Intensive phase regimens	5 (4-7)
Continuation phase regimens	3 (3-5)
Days on intensive phase treatment; Median (IQR) n=53	
Male	182 (154-186)
Female	184 (165-211)
Days on continuation phase treatment; Median (IQR) n=49	
Male	389 (185-503)
Female	522 (451-584)
HIV co-infection	31 (53%)
Male	19 (32%)
Female	12 (20%)
Unknown	3 (5%)
Proportion of HIV-positive persons on HAART*	13 (42%)
D4T/3TC/EFV	5 (16%)
AZT/3TC/EFV	3 (10%)
AZT/3TC/NVP	2 (6%)
TDF/3TC/EFV	2 (6%)
D4T/3TC/NVP	1 (3%)

* As percentage out of 31, which is the number of patients with HIV co-infection
IQR = interquartile range; HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; d4T = stavudine; AZT = zidovudine; 3TC = lamivudine; EFV = efavirenz; TDF = tenofovir disoproxil fumarate; NVP = nevirapine

Co-morbidities

Apart from HIV infection, the other co-morbidities that the researcher found in the patient sample included diabetes mellitus (2 patients); asthma (1 patient); hypertension (1 patient), and psychiatric disease (1 patient).

There were no reported cases of hepatic disease, peptic ulcer disease and renal disease. Being cognizant of the possibility of these co-morbidities right from the beginning of treatment is important because they could later be confused with drug-induced morbidity and may also influence the choice of specific regimens and dosages. This could confound the relationships between anti-TB drug exposure and the occurrence of an adverse event.

Distribution of the stages of treatment on the date of data collection

At the time of data collection, about one-fifth of the 59 patients were still in the intensive phase of DR-TB treatment, while the majority of the patients (66%) were in the continuation phase of DR-TB treatment (Figure 6.2).

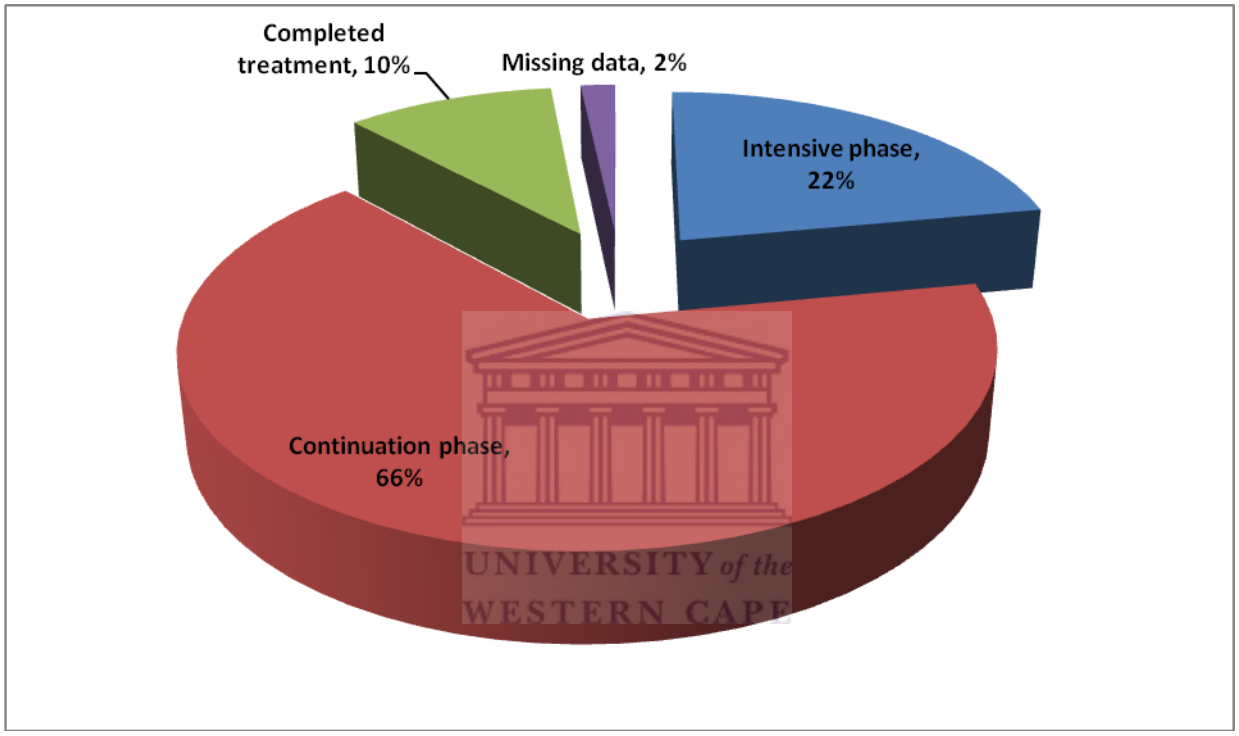


Figure 6.2: Distribution of patients according to the stage of treatment (N=59)

Individualization of DR-TB treatment

In the intensive phase of treatment, there were 30 unique regimens. This implied a high degree of individualized therapy of drug-resistant tuberculosis. Figure 6.3 shows that the three most commonly used regimens were:

1. AMK/CPX/ EMB/ ETO/ PZA, (17%)
2. EMB/ETO/ KM/ LFX/ PZA, (14%)
3. CS/ EMB/ ETO/KM/LFX/ PZA, (11%)

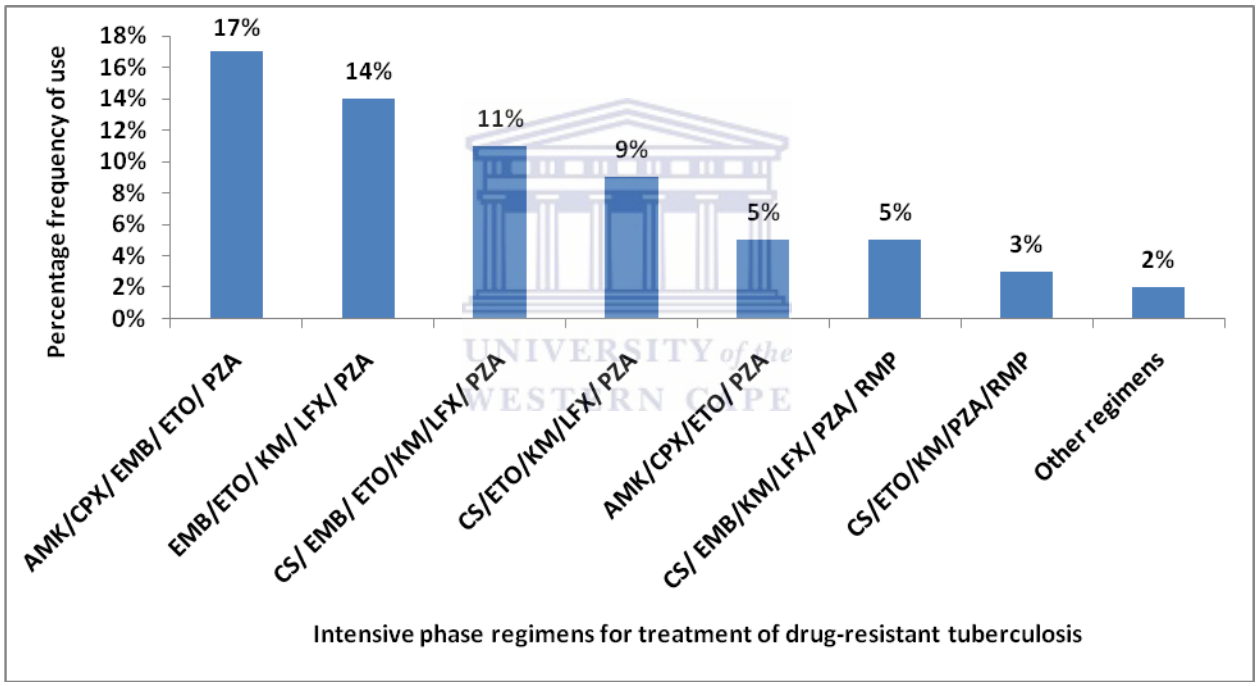


Figure 6.3: Distribution of DR-TB regimens used in the intensive phase of treatment

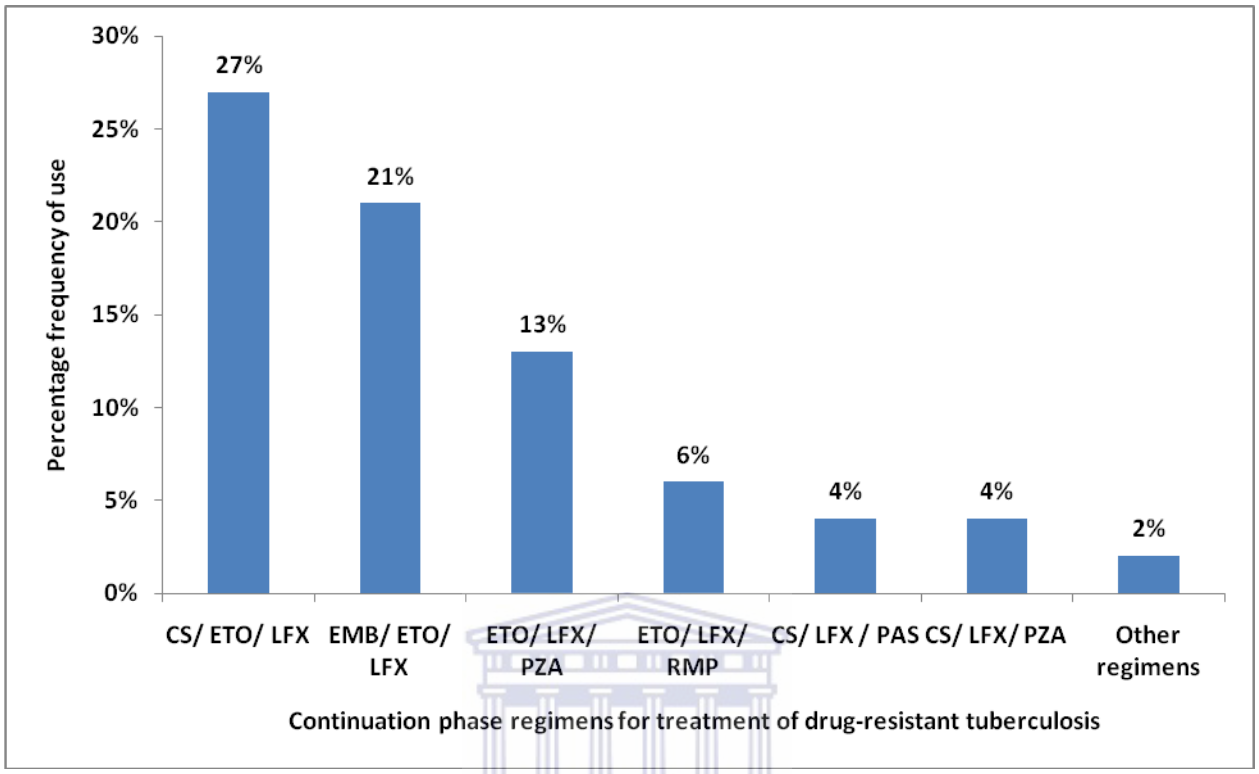


Figure 6.4: Distribution of DR-TB regimens used in the continuation phase of treatment

There were 18 unique regimens used in the continuation phase of treatment of drug-resistant tuberculosis. Figure 6.4 shows that the three most commonly used regimens were:

1. CS/ ETO/ LFX, (27%)
2. EMB/ ETO/ LFX, (21%)
3. ETO/ LFX/ PZA, (13%)

Frequency of the use of specific second-line anti-TB medicines

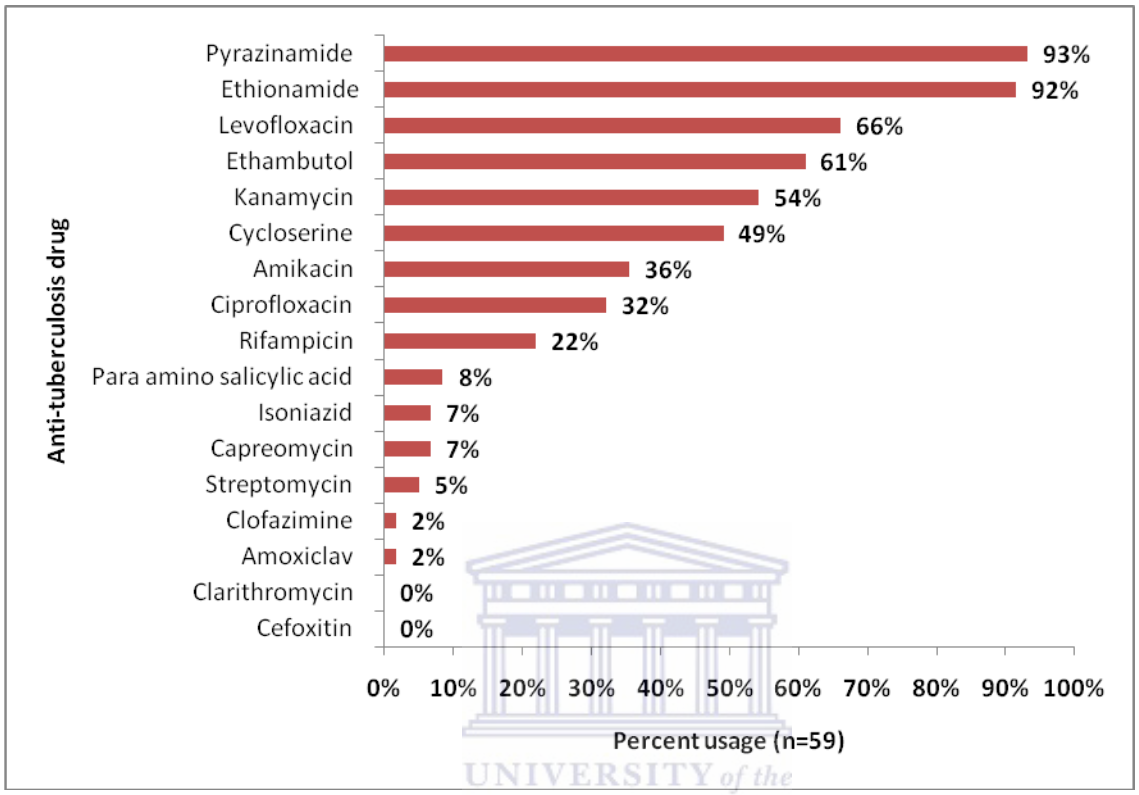


Figure 6.5: Frequency of the use of specific anti-TB medicines used for DR-TB treatment

Fifteen different anti-tuberculosis medicines were used by the patients included in the study (Figure 6.5). Most of the patients were treated with regimens containing pyrazinamide (93%) and ethionamide (92%). All patients were treated with an injectable anti-tuberculous agent (aminoglycoside or aminopeptide) during the intensive phase of treatment, with kanamycin being the most frequently used aminoglycoside (54%). Fluoroquinolones were used in almost all (98%) of the patients. Of these, levofloxacin (66%) was used twice as much as ciprofloxacin (32%).

Occurrence of adverse events during the treatment of drug-resistant tuberculosis

Fifty-three of the 59 patients experienced at least one adverse event, which is a 90% prevalence of adverse events. A total of 141 adverse events were reported by these patients. The number of adverse events experienced by an individual patient ranged from one to eight. The percentage of patients experiencing a given number of adverse events diminished between the intensive phase and the continuation phase of treatment (Figure 6.6). Almost all (87%) of these 141 adverse events were experienced during the intensive phase of treatment as shown in Table 6.4.

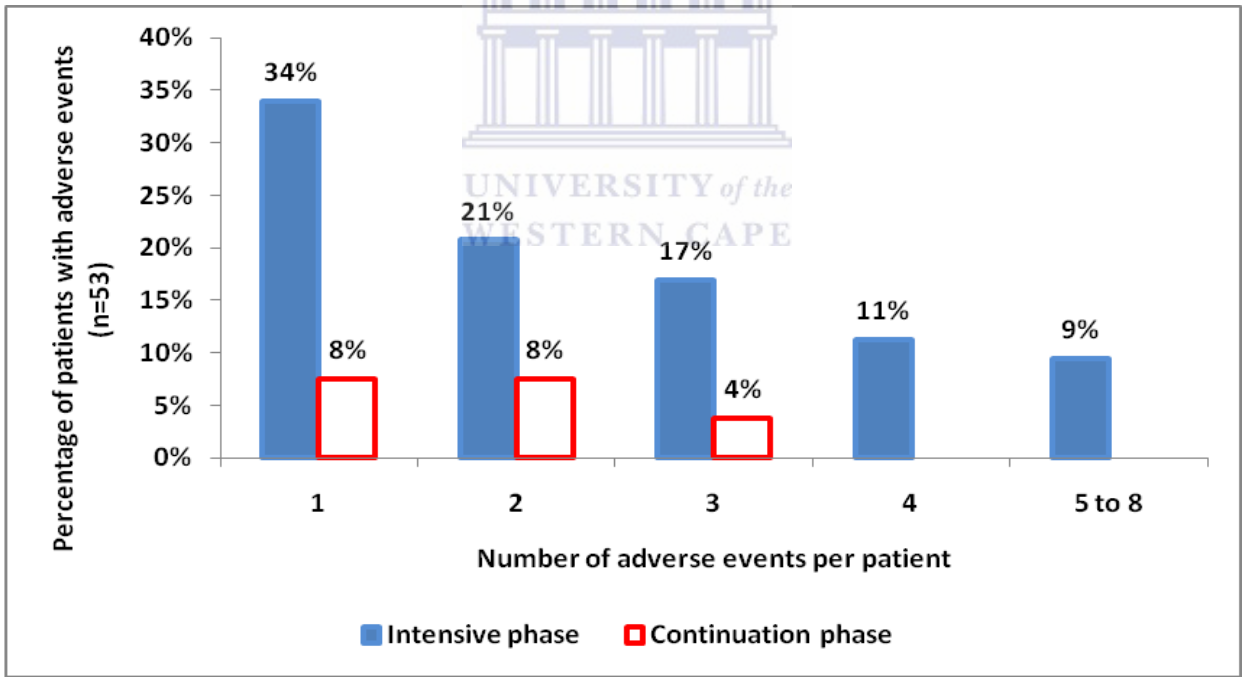
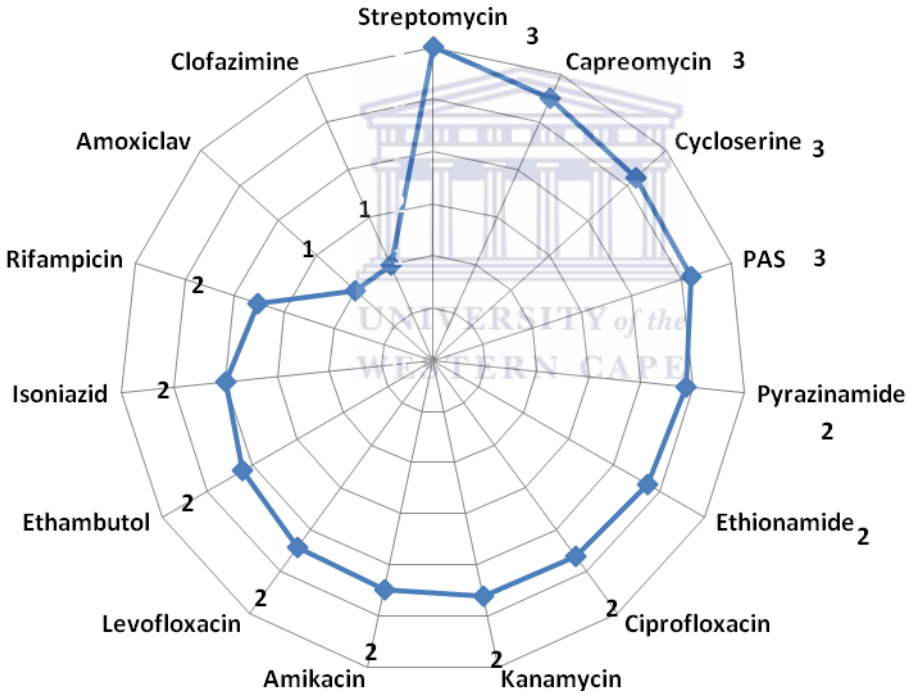


Figure 6.6: Frequency of number of adverse events per patient in the intensive and continuation phase of treatment

The average number of adverse events experienced by patients when using specific anti-tuberculosis medicines ranged from one to three. Patients who were on regimens that contained streptomycin, capreomycin, cycloserine and para-amino salicylic acid (PAS) experienced the highest average number of adverse events (3 adverse events per patient), while patients who were using amoxycillin/ clavulanic acid and clofazimine experienced the fewest, with an average of one adverse event per patient. The rest of the medicines were associated with a similar average number of two adverse events per patient (Figure 6.7).



PAS= para amino salicylic acid
Number next to a drug name indicates the mean adverse events experienced per patient treated with that drug

Figure 6.7: Average number of adverse events experienced per patient exposed to specific anti-tuberculosis drug

The three most frequently reported groups or specific types of adverse events were: ototoxicity (hearing loss and tinnitus), gastrointestinal tract (GIT)-related events and joint pain (Figure 6.8).

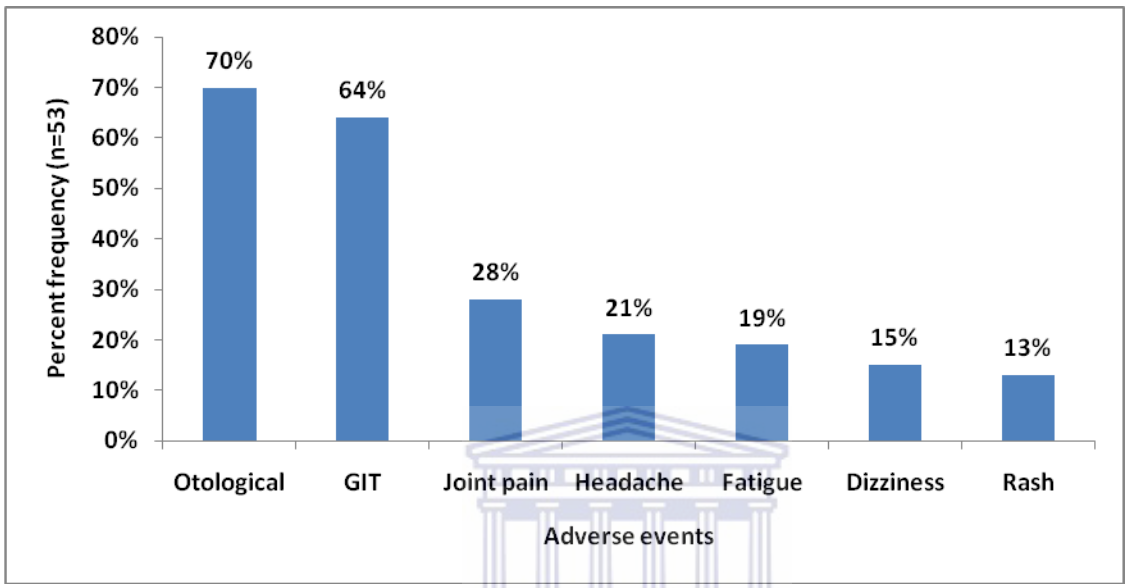


Figure 6.8: Overall frequency of the main adverse events during DR-TB treatment

The distribution of each type of adverse event between the intensive and continuation phases is shown in table 6.4.

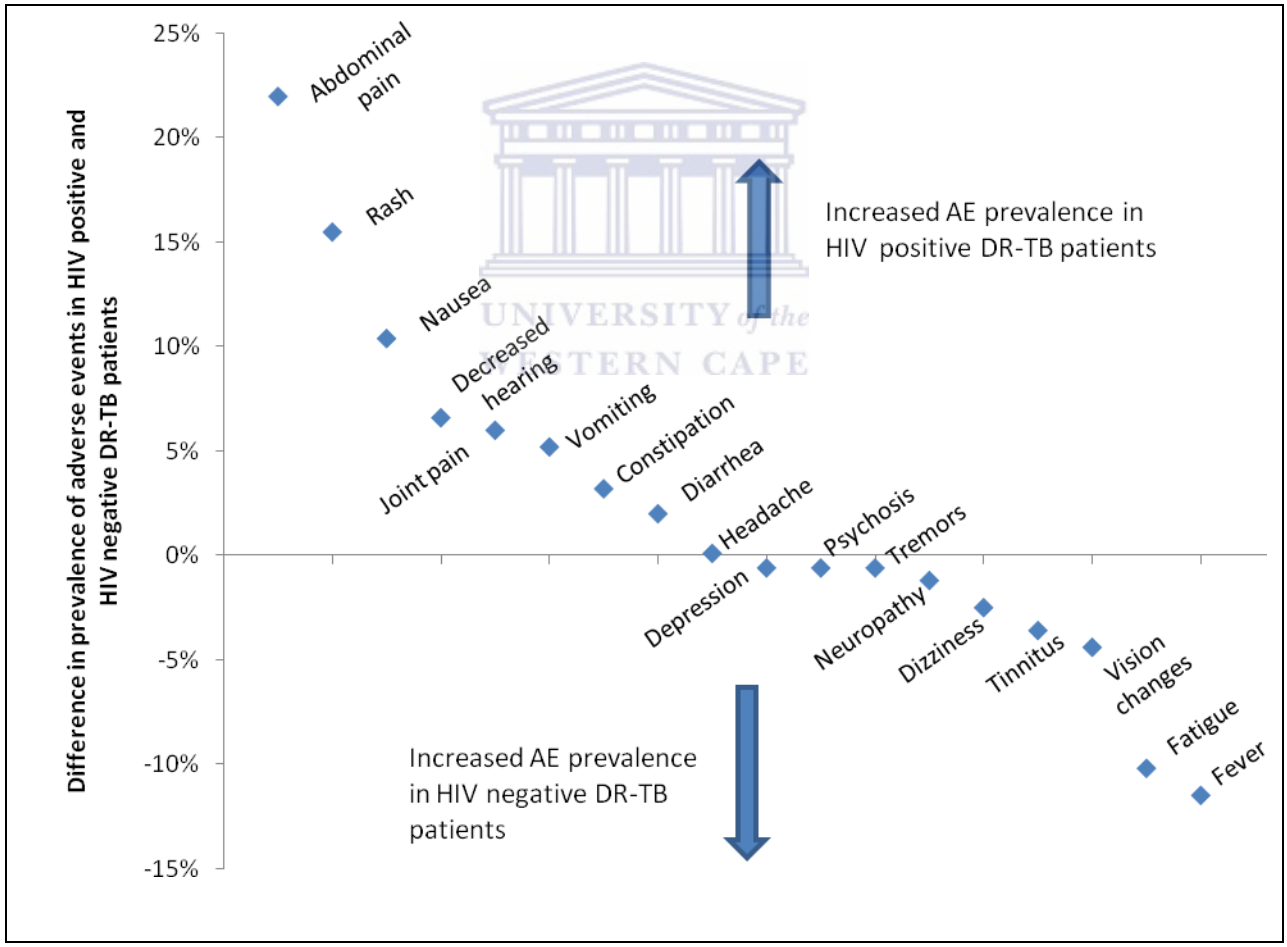
Table 6.4: Frequency of adverse events by treatment phase in the 53 patients who reported experiencing at least one adverse

Grouped adverse events	Specific adverse events	Both phases (N=53)*	%	Intensive phase (N=53)	%	Continuation phase (N=49) †	%
Hearing loss and Tinnitus	Tinnitus	24	45%	21	40%	3	6%
	Diminished hearing capacity	13	25%	12	23%	1	2%
	Sub-total	*37*	*70%*	*33*	*62%*	*4*	*8%*
GIT-related	Nausea	12	23%	8	15%	4	8%
	Abdominal pain	9	17%	8	15%	1	2%
	Vomiting	6	11%	6	11%	0	0%
	Diarrhea	5	9%	5	9%	0	0%
	Constipation	2	4%	2	4%	0	0%
	Sub-total	*34*	*64%*	*29*	*55%*	*5*	*10%*
Others	Joint pain	15	28%	13	25%	2	4%
	Headache	11	21%	10	19%	1	2%
	Fatigue	10	19%	8	15%	2	4%
	Dizziness	8	15%	7	13%	1	2%
	Rash	7	13%	7	13%	0	0%
	Neuropathy	4	8%	2	4%	2	4%
	Fever	3	6%	3	6%	0	0%
	Vision changes	3	6%	2	4%	1	2%
	Depression	2	4%	2	4%	0	0%
	Psychosis	2	4%	2	4%	0	0%
	Severe hepatitis	1	2%	1	2%	0	0%
	Decreased urine	1	2%	1	2%	0	0%
	Anemia	2	4%	2	4%	0	0%
	Loss of libido, delayed ejaculation	1	2%	0	0%	1	2%
Total of all adverse events		141		122		19	
Percent of all adverse events		100%		87%		13%	

*53 of the 59 patients reported experiencing at least one DR-TB treatment-related adverse event and 76% of the 53 patients had either completed or were still in the intensive phase of treatment at the time of data collection. †49 of the patients had progressed into the continuation phase of treatment and were either still in the continuation phase treatment or had completed treatment at the time of data collection. % = percent. The sum of column percentages may exceed 100% because a patient may experience more than one adverse event. GIT = gastrointestinal tract.

Differences in the prevalence of adverse events in HIV-infected and HIV un-infected patients

Five adverse events were more common among HIV-infected patients than among HIV-negative patients (the figure in bracket shows the excess frequency or the difference in absolute percentage frequency of adverse events between HIV-infected and HIV-uninfected patients): abdominal pains (22%); rash (16%); nausea (10%); diminished hearing capacity (7%), and joint pain (6%). By contrast, fever and fatigue are examples of adverse events that were reported less frequently by these patients (Figure 6.9).



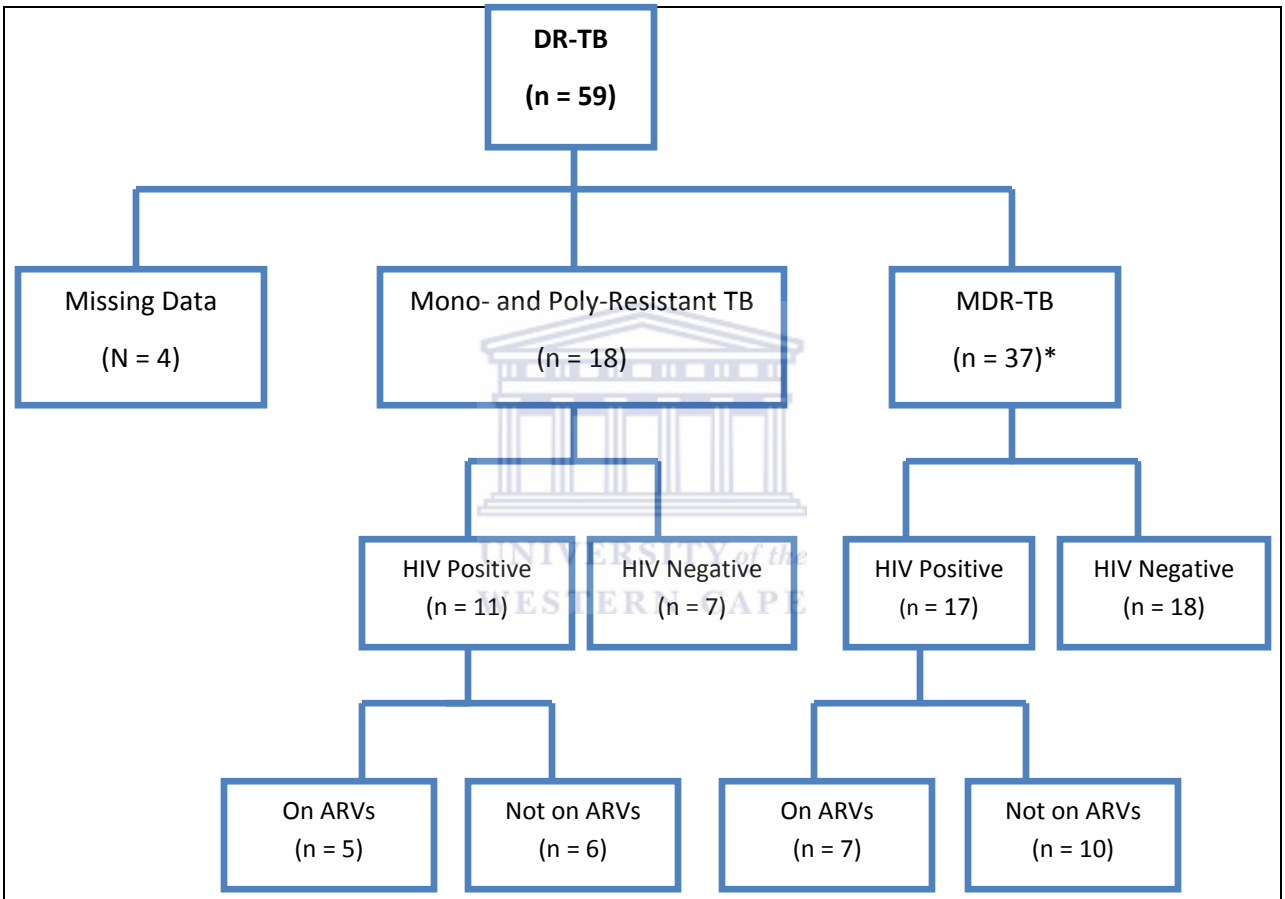
AE = adverse event; HIV = human immunodeficiency virus; DR-TB = drug-resistant tuberculosis

Figure 6.9: Comparison of the differences in the prevalence of adverse events in HIV-positive and HIV-negative DR-TB patients

While 73% of the moderate-to-severe adverse events lasted for more than 3 months, 60% of mild adverse events resolved themselves within 3 months of onset. Overall, in 53% of patients, the adverse events resolved within 3 months of onset, while 47% of patients experienced adverse events that persisted beyond 3 months. Adverse events were severe and warranted discontinuation of the suspected offending medicine in 4 out of 26 (15%) patients. Four out of the 42 (9%) patients for whom data was available recovered from their adverse reactions with sequelae (long-term medical complication).

Risk factor analysis

In this section, the findings of risk factor analysis are presented. Figure 6.10 is a flow chart that depicts how the researcher performed the sub-group analysis during risk factor analysis.



**Two (2) of the MDR-TB patients had unknown HIV status.*

Figure 6.10: Sub-groups of DR-TB patients by type of DR-TB, HIV status and ARV use

The researcher assessed the following seven risk factors for their influence on the occurrence of those general and specific adverse events that were associated with use of second-line anti-TB medicines:

1. Length of time on DR-TB treatment
2. HIV co-infection
3. ARV co-medication
4. Specific anti-TB medicines
5. Age
6. Gender
7. Baseline body weight

Risk factor analysis in all forms of DR-TB

The likelihood of occurrence of any adverse event, irrespective of its severity grading, was highest within the first two weeks of DR-TB treatment (OR 11.8; CI 1.3 - 104.7, p= 0.03), (Table 6.5).

Moderate-to-severe adverse events occurred mostly after 4 weeks of DR-TB treatment or after a much longer period of time (OR 6.4; CI 1.6 – 25.6, p=0.01). These adverse events were significantly associated with the presence of HIV co-infection (OR 3.1; 1.0 – 9.3; 0.04), (Table 6.5).

Adverse events lasting for more than 3 months occurred mostly after 4 weeks of treatment or after a much longer period of time (OR 9.6; CI 1.8 – 52.2, p=0.01), and were highest in patients co-infected with HIV (OR 3.9; CI 1.2 – 13.6, p=0.03) –particularly those patients on anti-retroviral co-medication (OR 7.9; 1.1 – 56.1, p=0.04). These long-lasting adverse events were also mostly associated with the use of ciprofloxacin-based DR-TB regimens (OR 4.0; CI 1.1 – 14.6, p=0.04), (Table 6.5).

On the other hand, adverse events that lasted for 3 months or less were mostly encountered within the first 4 weeks of DR-TB treatment (OR 5.9; CI 1.5 – 23.2, p=0.01). These short-duration adverse events were mostly associated with the use of levofloxacin-based regimens during treatment of DR-TB (OR 5.9; CI 1.6 – 21.5, p=0.01), (Table 6.5).

With regard to specific adverse events as shown in Table 6.6, the occurrence of fatigue was highest among young adults who were younger than 25 years old (OR 5.9; CI 1.2 – 28.1, p= 0.03). Gastrointestinal tract (GIT)-related adverse effects were mostly reported within the first 4 weeks of DR-TB treatment (OR 4.3; CI 1.3 – 14.7, p=0.02). The occurrence of nausea was significantly associated with the use of zidovudine (AZT)-based Highly Active Antiretroviral Therapy (HAART) (OR 7.5; CI 1.1 – 51.5, p= 0.04). Hearing loss and tinnitus were encountered particularly after 3 months of DR-TB treatment (OR 3.6; CI 1.1 – 12.3, p=0.04). Joint pains were significantly associated with the use of cycloserine-based regimens (OR 6.4; CI 1.6 – 25.8, p=0.01), while the risk of rash was significantly associated with the female gender (OR 15.9; CI 1.8 – 143.7, p=0.01).

Table 6.5: Risk factors for general adverse events in all 59 DR TB patients

Adverse event	Risk Factor	Odds Ratio (OR)	95% CI	p value
Any adverse event	Treatment duration of ≤ 2 weeks	11.8	1.3 - 104.7	0.03*
Moderate-severe adverse events	Treatment duration of ≥ 4 weeks	6.4	1.6 - 25.6	0.01*
	HIV co-infection	3.1	1.0 - 9.3	0.04*
Adverse events lasting > 3 months	Treatment duration of ≥ 4 weeks	9.6	1.8 - 52.2	0.01*
	HIV co-infection	3.9	1.2 - 13.6	0.03*
	ARV co-medication	7.9	1.1 - 56.1	0.04*
	Ciprofloxacin-based regimens	4.0	1.1 - 14.6	0.04*
Adverse events lasting ≤ 3 months	Treatment duration of ≤ 4 weeks	5.9	1.5 - 23.2	0.01*
	Levofloxacin-based regimens	5.9	1.6 - 21.5	0.01*

Table 6.6: Risk factors for specific adverse events in all 59 DR TB patients

Adverse event	Risk Factor	Odds Ratio (OR)	95% CI	p value
Fatigue	Age ≤ 25 years	5.9	1.2 - 28.1	0.03*
GIT adverse effects	Treatment duration of ≤ 4 weeks	4.3	1.3 - 14.7	0.02*
Nausea	AZT-based HAART	7.5	1.1 - 51.5	0.04*
Hearing loss and Tinnitus	Adverse events lasting > 3 months	3.6	1.1 - 12.3	0.04*
Joint pain	Cycloserine-based regimens	6.4	1.6 - 25.8	0.01*
Rash	Female	15.9	1.8 - 143.7	0.01*

Risk factor analysis in a sub-group of MDR-TB cases (n=37)

Among patients with MDR-TB (as shown in Table 6.7), HIV co-infection was more likely to be associated with a higher risk experiencing 3 or more adverse events (OR 8.0; CI 1.3 – 50.0, p=0.03). The risk of experiencing moderate-to-severe adverse events was even more pronounced in this sub-group of patients (OR 10.4; CI 1.6 – 66.9, p=0.02) as compared to the entire sample of 59 patients (OR 3.1; CI 1.0 – 9.3, p=0.04). These 3 or more adverse events were predominantly of a moderate-to-severe nature (OR 4.3; CI 1.1 – 17.4, p=0.04). The association of joint pain and use of cycloserine-containing anti-TB regimens maintained statistical significance in this sub-group of MDR-TB patients (OR

8.9; CI 1.6 – 49.8, p=0.01) and was higher than for the entire patient sample (OR 6.4; CI 1.6 – 25.8, p=0.01).

The risk of joint pain associated with the use of cycloserine-based MDR-TB regimens was even more pronounced among female HIV-positive patients who were using antiretroviral medication (OR 22.7; CI 2.2 – 237.4, p=0.01), (Table 6.8).

The concomitant use of cycloserine-based anti-TB therapy and efavirenz-based HAART were both statistically significant independent risk-factors for experiencing joint pain among patients with MDR-TB (Cycloserine: OR 15.7; CI 1.7 – 144.4, p=0.15; Efavirenz: OR 13.5; CI 1.0 – 178.3, p = 0.048), (Table 6.8).

Table 6.7: Univariate risk factor analysis in a sub-group of 37 patients with MDR-TB

Adverse event	Risk Factor	Odds Ratio (OR)	95% CI	p value
3 ≥ adverse events	HIV co-infection	8.0	1.3 – 50.0	0.03*
	ARV co-medication	0.2	0.0 – 1.6	0.13
	Moderate-severe adverse events	4.3	1.1 – 17.4	0.04*
Moderate-severe adverse events	HIV co-infection	10.4	1.6 - 66.9	0.02*
Joint pain	Cycloserine-based regimens	8.9	1.6 - 49.8	0.01*

Table 6.8: Multivariate risk factor analysis in a sub-group of 37 patients with MDR-TB

Adverse event	Risk Factor	Odds Ratio (OR)	95% CI	p value
3 ≥ adverse events	HIV co-infection	5.3	1.0 – 27.8	0.047*
	Efavirenz-based HAART	0.4	0.1 – 3.0	0.36
Moderate-severe adverse events	HIV co-infection	6.9	1.3 - 37.2	0.02*
	Efavirenz-based HAART	0.2	0.0 – 1.6	0.13
	Stavudine-based HAART	0.2	0.1 – 1.9	0.14
Joint pain	Cycloserine-based regimens	15.7	1.7 - 144.4	0.015*
	Efavirenz-based HAART	13.5	1.0 – 178.3	0.048*
Joint pain	Cycloserine-based regimens	22.7	2.2 - 237.4	0.01*
	HIV co-infection	3.4	0.4 – 27.5	0.26
	ARV co-medication	4.4	0. 3 – 68.7	0.30
	Female gender	1.1	0.2 – 6.6	0.95

Risk factor analysis in a sub-group of patients with mono- and poly-resistant TB (n=18)

The risk of experiencing moderate-to-severe adverse events was significantly associated with the use of ciprofloxacin-based anti-TB regimens (OR 16; CI 1.3 – 194.6, p= 0.03). These moderate-to-severe adverse events were hearing loss and tinnitus (OR 28.0; CI 2.1 – 378.9, p=0.01), in both HIV-positive and HIV-negative patients (Table 6.9).

Having a low baseline body weight (≤ 45 kgs) was a predisposing factor for decreased hearing (OR 36; CI 1.7 – 756, p=0.02) and gastrointestinal tract-related adverse events (OR 16.5; CI 1.1 – 250.2, p= 0.04) in patients who were being treated for mono- and poly-resistant tuberculosis (Table 6.9).

Ototoxicity (hearing loss and tinnitus) was significantly associated with the use of amikacin-based (OR 12.0; CI 1.3 – 111.3, p=0.03) as well as ciprofloxacin-based anti-TB regimens (OR 27.0; CI 1.9 – 368.2, p= 0.01). In addition, the use of ciprofloxacin-based anti-TB regimens was independently associated with the occurrence of tinnitus (OR 13.33; CI 1.1 – 169.4, p=0.04), (Table 6.9).

Table 6.9: Univariate risk factor analysis in a sub-group of 18 patients with mono- and poly-resistant DR-TB

Adverse event	Risk Factor	Odds Ratio (OR)	95% CI	p value
Moderate-severe adverse events	Ciprofloxacin-based regimens	16.0	1.3 – 194.6	0.03*
GIT-related adverse events	Baseline body weight ≤ 45 kgs	16.5	1.1 -- 250.2	0.04*
Decreased hearing	Baseline body weight ≤ 45 kgs	36.0	1.7 – 756.0	0.02*
Hearing loss and Tinnitus	Amikacin-based regimens	12.0	1.3 – 111.3	0.03*
	Ciprofloxacin-based regimens	27.0	1.9 – 368.3	0.01*
Tinnitus	Amikacin-based regimens	9.0	0. 8 – 108.3	0.08
	Ciprofloxacin-based regimens	13.3	1. 1 – 169.4	0.04*
Hearing loss and Tinnitus	Moderate-severe adverse events	28.0	2.1 – 378.9	0.01*

It is notable in Table 6.10 that the risk of decreased hearing in patients treated for mono- and poly-resistant tuberculosis was maintained in the multivariate logistic regression model that include the streptomycin as a covariate in the model (OR 33; CI 1.5 – 709, p=0.03). Note the instability and broadness of the confidence intervals, due to the small sample size.

Table 6.10: Multivariate risk factor analysis in a sub-group of 18 patients with mono- and poly-resistant DR-TB

Adverse event	Risk Factor	Odds Ratio (OR)	95% CI	p value
Decreased hearing	Baseline body weight ≤ 45 kgs	33.0	1.5 – 709.0	0.03*
	Streptomycin	2.3	0.0 – 157.8	0.70
Fatigue	Baseline body weight ≤ 45 kgs	18.2	0. 6 - 512.9	0.09
	Age ≤ 25 years	6.4	0. 4 - 116.6	0.21
	Male Gender	2.8	0.2 – 53.6	0.49
	Isoniazid-based anti-TB regimens	11.8	0.3 – 531.9	0.20

Table 6.11: Comparison of key risk factors between patients with mono- and poly-resistant TB and MDR-TB

Mono - and poly-resistant TB	MDR-TB
• Low baseline body weight (≤45 kgs) associated with increased risk of GIT-related adverse events and decreased hearing	• HIV co-infected individuals associated with increased risk of 3 ≥ adverse events and moderate-severe adverse events
• Amikacin and Ciprofloxacin-based anti-TB regimens associated with an increased risk of ototoxicity	• Cycloserine-based anti-TB regimens and Efavirenz-based HAART associated with increased risk of joint pain

Comparison of key risk factors for selected adverse events between HIV-infected and HIV-uninfected patients

The statistical significance of the association between joint pain and the use of cycloserine-based anti-TB regimens was maintained in a sub-group of HIV-infected patients (OR 7.5; CI 1.2 – 45.8, p=0.03). This association, however, lost its statistical significance among HIV-uninfected patients (7.5; CI 0.7 – 76.7, p=0.09), (Table 15).

The finding that hearing loss and tinnitus (ototoxicity) was of a moderate-to-severe nature in a statistically significant manner was maintained in both HIV-infected (OR 8.7; CI 1.7 – 45.2) and HIV-negative patients (OR 7.8; 1.2 – 52.3, p=0.03), (Table 6.12).

Note in Table 6.12 that HIV status is an effect-modifier for the association between the use of cycloserine-based DR-TB regimens and the occurrence of gastrointestinal tract-

related adverse events because the odds ratios for the HIV-positive and HIV-negative status are clearly different.

HIV status is a confounder for the relationship between the use of cycloserine-based DR-TB regimens and the occurrence of joint pains because the odds ratios are similar in both strata of HIV-infected and HIV-uninfected DR-TB patients.

In the same way, HIV status confounds the relationship between moderate-to-severe adverse events being caused by ototoxicity (hearing loss and tinnitus) because the odds ratios are similar in both strata of HIV status.

Table 6.12: Comparison of key risk factors between HIV-positive and HIV-negative DR-TB patients

HIV positive				HIV negative			
Adverse events	OR	95 CI	p value	Adverse events	OR	95 CI	p value
GIT-related Adverse events				*GIT-related Adverse events*			
Cycloserine	1.1	0.3 - 4.6	0.87	Cycloserine	10.3	1.0 - 103.7	0.048*
Nausea				*Nausea*			
Adverse events lasting < 1 month	21.3	1.7 - 263.7	0.02*	Adverse events < 1 month	cannot be calculated.		
Joint pain				*Joint pain*			
Cycloserine	7.5	1.2 - 45.8	0.03*	Cycloserine	7.5	0.7 - 76.7	0.09
Hearing loss/Tinnitus				*Hearing loss/Tinnitus*			
Moderate-severe	8.7	1.7 - 45.2	0.01*	Moderate-severe	7.8	1.2 - 52.3	0.03*

7. DISCUSSION

Prevalence of adverse events during treatment of drug-resistant tuberculosis

Adverse events, notably tinnitus, hearing loss, GIT-related adverse events and joint pains, were experienced by most (90%) of the patients included in the study. Most of the adverse events were reported in the intensive phase of treatment. Some differences in the occurrence of adverse events were observed in HIV-positive and HIV-negative patients respectively. Abdominal pain, rash, nausea, and decreased hearing and joint pain were among the adverse events more frequently reported by HIV-positive patients, whereas fever and fatigue were reported relatively less frequently (that is, they were reported most frequently among HIV-uninfected patients who were being treated for drug-resistant tuberculosis).

The 90% prevalence of adverse events in this study is higher than it is in other reported studies, where it ranged from 69%-86% (Nathanson, Gupta, Huamani *et al*., 2005; Bloss, Kuksa, Holtz *et al*., 2010; Seung, Omatayo, Keshavjee *et al*., 2009), but was lower than the 96% prevalence reported by Tupasi *et al*. in their study of 117 patients that was conducted in the Philippines (Tupasi, Gupta, Quelapio *et al*., 2009). While the reasons for this heterogeneity in the prevalence of adverse events related to DR-TB chemotherapy is unclear, it might be related to a variation in the use of specific anti-TB agents as well as in differences in co-morbidities and other covariates between study settings. The patient sample in this study is similar to those in other studies in terms of patient demographics, the number of second-line anti-TB medicines being used and the duration of treatment. In addition, treatment has proceeded in accordance with recommended guidelines (MoHSS, 2006, and WHO, 2010a). The HIV co-infection rate

and specific anti-TB agents used may however differ between settings. This should be borne in mind when interpreting and comparing results of adverse events reported from different countries. While this study's finding on the TB/HIV co-infection rate is higher than that reported in Europe and South East Asia where HIV prevalence rates are low (Leimane, Riekstina, Holtz *et al*., 2005; Lanternier, Dalban, Perez *et al*., 2007 and Cain, Kanara, Laserson *et al*., 2007), it is lower than the 80% co-infection rate observed for Lesotho, a country in Southern Africa with a very high prevalence rate of HIV infection (Seung, Omatayo, Keshavjee *et al*., 2009).

The frequency of tinnitus (45%) in the present study was higher than the 5.1%-24% range reported in the literature (Nathanson, Gupta, Huamani *et al*., 2005; Bloss, Kuksa, Holtz, *et al*., 2010; Tupasi, Gupta, Quelapio *et al*., 2009). The frequency of loss of hearing (25%) was within the range of 6.7%-33% that was reported in the literature (Tahaoglu, Torun, Sevim *et al*., 2001; Furin, Mitnick, Shin *et al*., 200); Bloss, Kuksa, Holtz *et al*., 2010; Tupasi, Gupta, Quelapio *et al*., 2009). The literature review shows that the reported rates of ototoxicity ranged from between 12% and 42% (Leimane, Riekstina, Holtz *et al*., 2005; Torun, Gungor, Ozmen *et al*., 2005; Seung, Omatayo, Keshavjee *et al*., 2009). This study found an almost double rate of ototoxicity in comparison to the 36% reported by Seung, Omatayo, Keshavjee *et al*., (2009), whose study population demographics, HIV prevalence and TB/HIV co-infection rates (although Lesotho's TB/HIV co-infection rates are generally higher than for this study population) were fairly comparable to this study's population. While it is still unclear as to why this should be so, one possible reason could be that the majority of the patients in the Seung study were still in the early stages of treatment, hence were exposed to relatively short periods of time to second-line anti-tuberculosis therapy (median of 252 days on treatment as compared to a median of 477 days for this study). Thus, not all of the potential adverse events may

have manifested at the time when they conducted and concluded their study. The high degree of heterogeneity of otological adverse events noted in the literature could have been brought about by differences in the use of specific ototoxic anti-TB medicines, varying exposure to other ototoxic medicines and environmental agents such as noise, as well as by the differences in the profiles of co-morbidities in the various patient population groups in the various studies.

Ototoxicity due to second-line anti-tuberculosis medicines

Ototoxicity (tinnitus and decreased hearing) is mainly associated with the use of parenteral anti-tuberculous agents, i.e. aminoglycosides and aminopeptides (Brummett and Fox, 1989; Nadol, 1993; de Jager and van Altena, 2002; Tan, Mulheran, Knox and Smyth, 2003; Duggal and Sarkar, 2007; and Selimoglu, 2007).

The drug-specific rate of patient-reported tinnitus in this study ranged from 33%- 50%, while loss of hearing function was 13%-67%. These findings are above the range of 15.4%-33% reported in studies conducted elsewhere (Tahaoglu, Torun, Sevim *et al.*, 2001; de Jager and van Altena, 2002; and Duggal and Sarkar, 2007).

The high rates of tinnitus and loss of hearing function found in this study might be attributable to the fact that none of the audiometry readings were validated by a qualified audiologist or a specialist Ear Nose and Throat (ENT) surgeon (Otorhinolaryngologist). In addition to this, there might have been some additive effects of interaction with other concomitant and potentially ototoxic anti-TB drugs that were used in the anti-TB regimens, such as fluoroquinolones and cycloserine. There is, moreover, the possibility of the interactive effects that arise from the presence of HIV disease and the concomitant use of antiretroviral medicines such as nucleoside reverse

transcriptase inhibitors (like zidovudine), which may also have contributed to this high rate of ototoxicity (Schouten, Lockhart, Rees, Collier and Marra, 2006; Katijah, 2010). All of these factors need further investigation so that the exact nature of these interactive effects can be determined.

Gastrointestinal tract-related adverse events during treatment of drug-resistant tuberculosis

Gastrointestinal tract (GIT)-related adverse events (64%) were the second most recorded group of adverse events. The specific adverse events that were recorded were: nausea (23%), abdominal pain (17%), vomiting (11%), diarrhea 9%, and constipation (4%).

The frequency of these specific GIT-related adverse events fall within the broad range reported in the literature (10.8%- 100%) (Furin, Mitnick, Shin *et al*., 2001; Nathanson, Gupta, Huamani *et al*., 2005; Leimane, Riekstina, Holtz *et al*., 2005; Torun, Gungor, Ozmen *et al*., 2005; Bloss E, Kuksa L, Holtz T H *et al*., 2010; Tupasi, Gupta, Quelapio *et al*., 2006; and Seung, Omatayo, Keshavjee, Furin, Farmer, and Satti, 2009). Since some studies have reported higher rates of specific GIT-related adverse events, it is possible that the patients in this study may have under-reported these adverse events during the course of their treatment.

Joint pain (arthralgia) during treatment of drug-resistant tuberculosis

Joint pain (28%) was the third most commonly reported adverse event. The findings of this study fall within (but more towards the upper side) the 6.7%-31% range that was reported in the literature (Torun, Gungor, Ozmen, *et al*.2005; Furin, Mitnick, Shin *et al*., 2001; Bloss E, Kuksa L, Holtz T H *et al*., 2010; and Tupasi, Gupta, Quelapio *et al*., 2006).

The variations in the reported occurrence could be attributed to the fact that the joint pains (arthralgia) were either reported ungraded (regardless of their severity grading, as was the case in this study), or else they were separately reported according to their severity grading for mild and severe joint pains – as was the case in the research conducted by Tupasi, Gupta, Quelapio *et al*., (2006).

Differences in the prevalence of adverse events in HIV-infected and HIV-uninfected persons treated for drug-resistant tuberculosis

The frequency of abdominal pains, nausea, rash, decreases in hearing function and joint pain was higher in patients with HIV co-infection. This observation is consistent with that cited in Lanternier, Dalban, Perez, Bricaire, Costagliola and Caumes (2007), who found the risk of adverse events was higher in TB patients co-infected with HIV (OR 3.9 95% CI 2.1 – 7.5, p< 0.001).

However, because of the descriptive design of this study, the researcher was unable to establish and conclude associations from these relative adverse event frequencies in DR-TB patients co-infected with HIV. The researcher therefore proposes an appropriate analytic design to further elucidate these identified associations.

It was necessary for the researcher to consider the possibility of drug-drug interactions (Papastavros, Dolovich and Holbrook, 2002), drug-disease interactions, and disease-disease interactions in the present study, particularly since an average of 5 different anti-TB agents were used by each patient in the study and that over 50% of the patients were co-infected with HIV (42% of these HIV co-infected patients were on additional antiretroviral medications).

Impact of adverse events on the continuity of treatment of drug-resistant tuberculosis

In this study, the researcher found that in 15% of the patients, the adverse events were so severe that they warranted the discontinuation of the suspected offending medicine. This rate of this discontinuation is lower than that reported in the literature (Nathanson, Gupta, Huamani *et al*., 2005; Tahaoglu, Torun, Sevim *et al*., 2001; Shin, Pasechnikov, Gelmanova *et al*., 2007; and Bloss E, Kuksa L, Holtz T H *et al*., 2010).

This study's findings are nevertheless similar to those of Furin, Mitnick, Shin, *et al*. (2001), namely that because the patient was able to tolerate and bear the adverse events of the anti-TB medicines, these specific adverse events did not cause any discontinuation of the treatment apart from the occasional suspension of an offending agent in 11.7% of the patients.

Risk-factors for the occurrence of adverse events during treatment of drug-resistant tuberculosis

The researcher examined several risk factors in this study. This section provides an in-depth discussion of the main findings about the risk-factors that were associated with the occurrence of adverse events in patients on DR-TB treatment, in the context of the available body of knowledge.

Length of time on DR-TB treatment

The first two weeks of DR-TB treatment were associated with the highest risk of an occurrence of any adverse event, while moderate-to-severe adverse events were mostly experienced after 4 weeks of DR-TB treatment.

These findings are consistent with those reported by Sharma, Mohan and Kadhiravan (2005), who found that the majority of adverse events experienced during treatment of DR-TB occurred within the first 2 months (or 8 weeks) of treatment.

HIV co-infection and increased risk of serious or moderate-to-severe adverse events in the treatment of MDR-TB

In this study, the researcher found that DR-TB patients, who were co-infected with HIV, had a higher risk of experiencing three or more adverse events, most of which were moderate-to-severe in nature. This finding is already reported in the literature.

Marks and his colleagues found that, in a South African population of tuberculosis patients co-infected with HIV, serious adverse events (SAEs) during anti-tuberculosis therapy occurred more frequently in HIV co-infected patients than they did in HIV-uninfected patients (26.7% versus 13.3% p=0.003) (Marks, Dheda, Dawson, Ainslie and Miller, 2009). Similarly, the study conducted by Breen, Miller, Gorsuch, Smith, Schwenk, Holmes *et al*., (2006) found that serious adverse events occurred more frequently in TB patients who were co-infected with HIV (40% serious adverse reactions in HIV-positive patients versus 26% in HIV-negative patients, p=0.008).

In addition to this, Sharma and colleagues noted that HIV-positive persons are more prone to anti-TB treatment-related adverse events and the risk of an increased possibility of adverse events with the presence of advanced immune suppression (Sharma, Mohan and Kadhiravan, 2005). Other studies that have reported similar findings are those undertaken by Cohen and Meintjes (2010) and Abex, Varella, Siqueira, and Mello (2010).

ARV co-medication and the risk of serious or severe adverse events during DR-TB treatment

This study found that HIV-infected DR-TB patients who were concomitantly treated with antiretroviral medication (and particularly with efavirenz-based HAART) were at an increased risk of experiencing moderate-to-severe adverse events. What is most notable is that there seems to be an interactive effect that increases the risk of joint pains among patients who are concomitantly being treated with efavirenz-based HAART and cycloserine-based DR-TB treatment regimens.

Whereas the concomitant use of antiretroviral and anti-tuberculosis medications is known to be associated with an increased risk of occurrence of serious, treatment-related adverse events (Venkatesh, Swaminathan, Andrews and Mayer, 2011), the researcher was unable to identify any study that specifically reported an association between increased joint pains (arthralgia) in patients who were being treated for HIV with efavirenz-based HAART.

However, according to an online data base maintained by eHealthMe that tracks and analyses medication-related adverse events, 1.72% of the 5,276 people who reported experiencing side effects while taking efavirenz-based HAART had arthralgia, as of June 07, 2011 (eHealthMe, 2011).

This association is further corroborated by a post-marketing follow-up reported by Merck Sharp and Dohme (MSD), the original innovators and manufacturers of efavirenz (MSD, 2006). Because post-marketing medicine safety data are reported voluntarily from a population of unknown size, accurate estimates of the prevalence and the risks of occurrence of the reported adverse events cannot be made.

Zidovudine-based HAART and the risk of nausea during DR-TB treatment

There was an increased risk of nausea (which lasted less than a month) among patients treated for drug-resistant tuberculosis and who were concomitantly treated for HIV infection using zidovudine-based HAART.

This finding is not new because zidovudine (AZT) is known to cause nausea, and this particular association has been extensively described in the literature. In the randomized clinical trial conducted by Spruance, Pavia, Mellors, Murphy, Gathe, Stool *et al*., (1997), nausea and vomiting were more common in patients who were receiving zidovudine than they were among patients receiving stavudine. This association has also been reported by Carr and Cooper (2000).

Young adult age (≤ 25 years) and risk of fatigue in DR-TB treatment

In this study, the risk of fatigue was found to be highest among young adults who were 25 years old or younger.

The researcher found no data available in the literature consistent with this finding, among patients being treated for DR-TB. The available evidence, which is based on first-line anti-tuberculosis drug regimens, was not specific for the association of patient age and fatigue. It indicated, instead, that the overall risk of adverse events increases among elderly persons who are over 60 years old (adjusted hazard ratio, 2.9; 95% CI, 1.3 to 6.3, Yee, Pelletier, Parisien, Rocher and Menzies, 2003).

Among 1,317 patients on first-line anti-tuberculosis treatment, the frequency of drug reactions increased from 2.3% at ages 0–19 to 4.6% at ages 20–39, 7.1% for ages 40–59

and to 8.4% for those who were 60 years old and above (Ormerod and Horsfield, 1996). The clinical significance of this finding is therefore unclear, and could have been a spurious statistical finding with no underlying biologically plausible explanation.

Female gender and the risk of skin rash in DR-TB treatment

The females in the sample were found to be at a higher risk of experiencing skin rash.

No data was available from the reviewed literature that indicated a specific association between female gender and the risk of skin rash in patients who were being treated for drug-resistant tuberculosis.

There were, however, various studies that reported that females, in particular, were at risk for the occurrence of adverse events of any kind among patients on both first-line and second-line anti-tuberculosis treatment. Being female was associated with an increased risk (OR = 1.6, 95%CI: 1.9–36.4) of experiencing an adverse event in patients being treated for pulmonary tuberculosis, irrespective of the type of drug-resistance of the infecting tubercle bacilli (Javadi, Shalviri, Gholami, Salamzedeh, Maghooli and Missaeedi, 2007).

There is therefore a need for future research to verify the finding that there is an increased risk of skin rash for females, during treatment of drug-resistant tuberculosis using second-line anti-tuberculosis treatment.

Low baseline body weight and the risk of adverse events during DR-TB treatment

This study found that patients with a low body weight (≤45 kilograms) at the start of DR-TB treatment (i.e. underweight adults) in the sub-group of patients being treated for

mono- and poly drug-resistant *M. tuberculosis*, were associated with an increased risk of experiencing decreased hearing and GIT-related adverse events.

However, few of the reviewed studies have reported findings based on patient body weight. In the study that was conducted by Kigen, Kimaiyo, Nyandiko, Faragher, Sang, Jakait, *et al*. (2011), baseline body weight was reported as a risk-factor for an increased risk of clinically significant drug-drug interactions in patients on antiretroviral therapy.

The majority of other relevant studies have used the body mass index instead of patient body weight. None of the reviewed patient records in this study contained information on patient height because this measurement is not routinely taken at the study site. The researcher, therefore, was unable to calculate the body mass index for risk factor analysis for this study, and for comparison with other studies.

Cycloserine-based anti-tuberculosis regimens and risk of joint pain (arthralgia) during DR-TB treatment

According to data for this study, the use of cycloserine-based anti-TB regimens was associated with an increased risk of joint pain (arthralgia).

There was no study in the literature that specifically reported an association between the use of cycloserine (either alone or as part of an anti-tuberculosis regimen) and occurrence of joint pain. Almost all of the reviewed relevant studies and reports highlighted the occurrence of adverse neuropsychiatric events that are associated with the use of cycloserine (Weyer, 2005; Arbex, Varella, de Siqueira and de Mello, 2010).

On the other hand, pyrazinamide and fluoroquinolones are two types of second-line anti-tuberculosis medicines well known to be associated with occurrence of joint pain (Weyer, 2005).

Although the finding of an association between the use of cycloserine-containing anti-TB regimens and joint pain is an interesting one, it raises even more questions about the nature and biological plausibility of this association if one considers the role of pyrazinamide and the two fluoroquinolones (ciprofloxacin and levofloxacin).

In a further stratified analysis of the data, the relative risk of pyrazinamide and joint pain was 1.02 (p=0.57), and this increased to 1.27 (p=0.75) in a sub-group of patients on cycloserine-based anti-TB regimens. The relative risk for the sub-group of patients on non-cycloserine-containing regimens could not, however, be determined because one of the cross-tabulated cells contained a zero value.

Although the relative risks in both analyses were not statistically significant, the point estimate for the sub-group of concurrent pyrazinamide and cycloserine users was higher than for that of the pyrazinamide only users. This could be an indication of an interaction or effect modification between pyrazinamide and cyloserine and the occurrence of joint pain.

Additionally, there could be a pharmacologic interaction between the use of cycloserine and efavirenz, which augments the risk of joint pain as has been previously discussed under the section on antiretroviral co-medication and the risk of serious adverse events during treatment of drug-resistant tuberculosis.

But because of the small sample size used in this study, such an association cannot be concluded and can only be regarded as a hypothesis generated by the study. Larger samples will be required before such sub-analyses can be undertaken. Strom *et al*. (2005) emphasizes that effect modification (or interaction) is useful for generating a new hypothesis and that it should always be pursued if it is identified during the analysis of data.

Amikacin and ciprofloxacin-based anti-tuberculosis regimens and the risk of ototoxicity during DR-TB treatment

The use of amikacin and ciprofloxacin-based regimens were both independently associated with an increased risk of ototoxicity (i.e. hearing loss and tinnitus). This finding of ciprofloxacin being a possible risk-factor for ototoxicity should be treated with caution, given that 18 (95%) of the 19 patients who were prescribed ciprofloxacin were also prescribed amikacin for their individualized anti-TB regimens ($p<0.001$)

The co-prescription of amikacin and ciprofloxacin could be one of the reasons that explain this joint relationship, although both amikacin (an aminoglycoside) and ciprofloxacin (a fluoroquinolone) are independent aetiologic agents for ototoxicity (Brummett and Fox, 1989; Nadol, 1993; de Jager and van Altena, 2002; Tan, Mulheran, Knox and Smyth, 2003; Duggal and Sarkar, 2007; and Selimoglu, 2007).

The role of ciprofloxacin and other fluoroquinolones in causing ototoxicity appears to be unclear and doubtful. Evidence in the literature seems to point that topical use of ciprofloxacin and fluoroquinolines does not cause damage to the inner ear, although

researcher could not find a definitive paper that has evaluated the long-term use or oral ciprofloxacin and other fluoroquinolones and ototoxicity (Mudd *et al*., 2010).

The literature confirms that amikacin and other aminoglycosides are known to cause ototoxicity (Arnold, Brouse, Pitcher and Hall II, 2010; Arbex, Varella, de Siqueira and de Mello, 2010; Mudd *et al*., 2010).

Strengths and limitations of the study:

Strengths of the descriptive design

The data for this study reflects real-life DR-TB treatment practices and patient experiences. The cross-sectional descriptive design enabled the researcher to examine and describe the prevalence and profile of adverse events in the patient sample. Because of this, the researcher was able to generate the tentative hypothesis that some adverse events occur more frequently in DR-TB patients who are co-infected with HIV – a fact that is clinically important when treating this sub-group of patients.

Limitations of the descriptive design

By making use of retrospective data, the researcher encountered instances of missing patient treatment records and missing data about specific variables. In addition to this, it was not possible to perform a qualitative causality assessment of the adverse events by using the available data, especially in view of the paucity of the laboratory data.

It was also necessary to consider the possibility of the selective or under-reporting of adverse events by patients. Some symptoms of the reported adverse events, such as nausea, may have overlapped with symptoms of HIV/ AIDS or the adverse effects of antiretroviral medicines (Venkatesh, Swaminathan, Andrews and Mayer, 2011).

The small sample size and the use of data from one facility alone may not allow for generalization of findings beyond the studied sample, and this is one notable limitation of the study.

Analytic study design: The cross-sectional nature of the study was inherently limited in its ability to assess the time-to-adverse event risk profile of the adverse events identified in this study. Another major limitation of the study was the inability of the cross-sectional design to confirm the temporal sequence of exposure and outcome because both exposure and outcome were measured at the same point in time (Beaglehole, Bonita and Kjellstrom, 1993).

Sample size and study power: The study made use of a small sample size (n=59), and for this reason it was not suitable for the detecting serious adverse effects, most of which occur quite rarely. This limitation therefore increased the possibility of Type II errors, namely, the failure of the study to detect significant findings in those cases where they truly exist. In addition to this, the small size of the sample did not permit a detailed sub-group analysis for risk-factor identifications because some of the sub-groups had either too few or zero numbers.

Measurements: The retrospective nature of data collection may have, to some extent, rendered it incapable of accurately and comprehensively measuring the various variables of interest in this study.

Moreover, the researcher did not conduct causality assessments for individual patient medicine and adverse-effect combinations in this study, and also did not assess drug-drug interactions with ARV medicines. Similarly, since the severity grading was based on the MoHSS TB guidelines, it may not have been comparable with the grading schemes that were used in other studies.

The pre-defined list of 19 adverse effects (Appendix 6) that are routinely monitored by clinicians who are treating patients on MDR-TB treatment may have biased clinicians against looking out for any of the other potential adverse effects that were not included on this list. In addition to this, this study did not quantify medicine exposure in terms of the total dose administered – as calculated from the dose, frequency and duration of treatment of each respective medicine.

The specific medicines used in the prior treatment of tuberculosis and the previous adverse effects that were experienced by patients whose records were reviewed, were not examined. Information about the previous experiences of patients with first-line TB medicines and other treatment regimens was missing.

The laboratory monitoring of key organ functions such as those of the liver and kidney, appears not to have been carried out in a structured and regular manner. This may have reduced the chances of detecting any hepatic and renal damage.

The symptomatic description of some of the less objective adverse events, such as fatigue or dizziness, was not specific enough to describe a particular adverse effect.

The time before the onset of adverse effects and their duration, may not have been precisely determined in the way that they were documented in the patient treatment records.

Generalisability of findings: The findings of this study may not be generalized to the whole of Namibia because of the possible non-representativeness of this single-site study sample. A study with a more representative sample that includes other drug-resistant tuberculosis treatment sites is therefore necessary in order to obtain more generalisable findings.

8. CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The prevalence of adverse events in the patients included in this study was 90%. A range of adverse events are frequently experienced by patients on second-line anti-tubercular treatment, especially during the intensive phase of treatment.

In the studied setting, the most frequently observed adverse events during treatment of DR-TB were the following: ototoxicity (decreased hearing and tinnitus) (70%); gastrointestinal disorders (64%); joint pain (28%); headache (21%); fatigue (19%); dizziness (15%) and rash (13%). Some adverse events such as abdominal pains, rash and nausea were more frequently observed in HIV-infected DR-TB patients than among HIV-uninfected ones.

The observed adverse events were tolerated by 85% of the patients. Most of these adverse effects were mild and either resolved by themselves within 3 months of treatment and without need for intervention, or required only symptomatic and adjuvant treatment. Most of the patients recovered from these adverse effects without any known serious medical consequences.

A number of risk factors that are associated with the occurrence of adverse events in patients treated for DR-TB were identified. The first two weeks of DR-TB treatment were associated with the highest risk of adverse events. Moderate-to-severe adverse events were mostly experienced after four weeks of DR-TB treatment. Drug-resistant TB patients who were co-infected with HIV were more prone to experiencing three or more adverse events. Patients who were co-treated with efavirenz-based HAART were at an

increased risk of experiencing moderate-to-severe adverse events, notably joint pains (arthralgia). Those treated with zidovudine-based HAART were at an increased risk of experiencing nausea. Females were associated with an increased risk of skin rash.

Among patients who were treated for mono-and poly-drug-resistant TB, those with a low baseline body weight (≤45 kilograms) were at an increased risk of decreased hearing and suffering from adverse gastrointestinal events. The use of cycloserine-based DR-TB regimens was a risk factor for joint pain, while the use of amikacin-containing and ciprofloxacin-containing regimens was associated with an increased risk of ototoxicity.

An accurate knowledge of the risk factors associated with particular adverse reactions by patients to medicines will help doctors and other clinicians to design interventions to prevent or minimize the future occurrence of medication-related adverse effects in patients (Pirmohamed, Breckenridge, Kitteringham & Park, 1998; Riedl & Casillas, 2003). This study, therefore, was able to generate the information that was needed about the types, frequency, characteristics and risk-factors associated with adverse events of drug-resistant anti-TB chemotherapy so that clinicians could make informed choices about the attention, resources and efforts that would be needed for the prevention and clinical management of the serious adverse reactions that are frequently caused by second-line anti-TB medicines, as recommended by Zaleskis (2006).

Most importantly, the findings of the risk factor analysis should be interpreted with caution because of the low sample size which severely restricted the scope of this study. Nonetheless, the National Tuberculosis Control Program should continue to encourage

clinicians who are treating DR-TB patients to closely monitor, document and manage adverse events with second-line anti-TB therapy.

Therefore, clinicians should pay particular attention to monitoring, preventing and managing adverse events in patients on DR-TB therapy, especially during the intensive phase of treatment and in HIV co-infected patients, so as to minimize treatment-related intolerance and morbidity; and optimize patients' adherence to treatment and the outcomes of drug-resistant tuberculosis therapy.

Recommendations

Policy and Practice: Except for serious ototoxicity, most of the medicines used in second-line TB treatment regimens are associated with generally tolerable and manageable adverse events. The current practice of close and regular monitoring of adverse events of TB chemotherapy at the study facility is highly commendable and should be encouraged so that the adverse events can be detected and managed sufficiently early to prevent any serious injury to patients.

The careful, intensive, aggressive and close follow-up of patients, especially during the intensive phase of second-line TB chemotherapy for the early detection and management of serious adverse events should be considered by clinicians and the TB program managers.

Before discharging patients from the hospital after the completion of the intensive phase of treatment, patients should be counseled on the nature of the adverse medication

effects that they might expect during their continuation phase of second-line anti-tuberculosis treatment, and they should be told what to do if they find that they do in fact experience such treatment-related adverse effects.

Future research:

A longitudinal, prospective observational design should be applied to quantify the magnitude of risk and determine the time-profile of the risk of the serious adverse effects of second-line anti-TB regimens, particularly ototoxicity.

The association of joint pain and use of cycloserine should be verified by subsequent studies using designs that are appropriate for proving causation.

The two important research questions arising from this research, which may be pursued in follow-up studies, are:

1. Does the concomitant use of pyrazinamide, cycloserine and efavirenz increase the risk of joint pain (arthralgia) during treatment of drug-resistant tuberculosis?

2. Does the concomitant use of a fluoroquinolone antibiotic, an aminoglycoside and a nucleoside reverse transcriptase inhibitor (NRTI) increase the risk of ototoxicity during treatment of drug-resistant tuberculosis?

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10. APPENDICES

Appendix 1: Data collection form and coding scheme

S.N	Variable	Categories and Codes
1.	Unique Identification No.	[Text string]
2.	Date of Birth (DoB)	DD/MM/YYYY
3.	Date of registration in TB clinic (DoR)	DD/MM/YYYY
4.	Date of admission in TB ward	DD/MM/YYYY
5.	Age at registration in TB clinic	Years = (DoR-DoB)
6.	Recorded age	
7.	Gender	1. Male 2. Female
8.	Initial Wt in kg	###_____ kg
9.	Initial BMI	
10.	Employment/ profession/ occupation	
11.	Mother tongue (14 Language Options)	Oshiwambo, Damara-Nama, Herero, Afrikaans, English, Thimbukushu, Rukwangali, Rumanyo/ Rugciriku, Subiya, Silozi, SeTswana, German, Other, Missing

12.	Type of TB disease	1. PTB smear + 2. PTB smear – 3. EPTB 4. Other, specify
13.	TB diagnostic category	New patient, never treated for TB Previously treated with 1st line meds Previously treated with 2nd line meds
14.	Resistance pattern of Mycobacterium at diagnosis	1. Poly resistance 2. MDR 3. XDR 4. Data not available
15.	Date intensive TB treatment was started (DoiStart)	DD/MM/YYYY
16.	Date continuation TB treatment was started (DocStart)	DD/MM/YYYY
17.	Date TB treatment stopped (DotxStop)	DD/MM/YYYY
18.	Duration of intensive phase treatment	Days= (DocStart- DoiStart)
19.	Duration of continuation phase treatment	Days= (DotxStop - DocStart)
20.	Total treatment duration	Days= (DotxStop - DoiStart)

17.	Treatment regimen	Amikacin, Capreomycin, Cefoxitin, Clarithromycin, Cycloserine, Ethambutol Ethionamide, Kanamycin, Levofloxacin, Para-aminosalicylic acid, Pyrazinamide, Streptomycin, Isoniazid, Rifampicin
18.	Number of medicines in the intensive phase of TB regimen	• 4 • 5 • 6 • 7 • 8 and more
19.	History of change in TB treatment regimen	• Yes • No
20.	Reason for change in TB treatment regimen	• Adverse effects • Treatment failure • Others, specify
21.	Concomitant medications	ARVs (specify) , Pyridoxine, Cotrimoxazole, Contraceptives, other (specify)
22.	HIV status	• Positive • Negative • Unknown
23.	Other Co-morbidities/ Conditions	Diabetes, Hypertension, Asthma, Peptic ulcers, Renal disease, Hepatic disease, Psychiatric disorder, Drug and alcohol abuse, Other (specify)

24.	Occurrence of adverse reaction	• Yes • No
25.	Treatment phase when ADR occurred	1. Intensive phase 2. Continuation phase 3. Not applicable
26.	Date of onset of ADR (D_onset)	DD/MM/YYYY
27.	Days to onset of ADR	
28.	Brief description of the adverse reaction/s e.g. rash on the skin	Text Consider Coding using the WHO-ART codes of system organ class/ preferred terms
29.	Relevant Laboratory evidence (values)	
30.	Duration of ADR	
31.	Severity grading of the ADR	1. Mild; requiring no intervention 2. Moderate; requiring intervention 3. Severe; requiring change in treatment or hospitalization 4. Fatal
32.	Outcome of ADR	List of outcomes

Adapted from the MDR-TB Patient Treatment Card. MoHSS, 2006: 184 (Annexure 17)

Appendix 2: Study Approval by the Higher Degrees Committee of the University of the Western Cape

Private Bag X17, Belville, 7535
South Africa
Tel: +27 (0) 21 959 2163
Fax: +27 (0) 21 959 2755
E-mail: csjohnson@uwc.ac.za

HIGHER DEGREES COMMITTEE

8 December 2009

TO WHOM IT MAY CONCERN

Dear Sir/Madam

Research Project of Mr Evans Sagwa (Student Number: 2831700)

This letter confirms that **Mr Sagwa** is a registered student in the Faculty of Community and Health Sciences at the University of the Western Cape.

His research proposal entitled *"Prevalence and risk factors for occurrence of adverse effects of second line anti-tuberculosis medicines amongst patients on TB chemotherapy in a treatment facility in Namibia: 2009-10"* submitted in fulfilment of the requirements for Masters in Public Health has been examined by the Higher Degrees Committee and found to be of high scientific value, methodologically sound and ethical.

Senate Higher Degrees and Senate Ethics Committees have approved the proposal.

We fully support the research.

Sincerely

DR GAVIN REAGON
Chairperson: Higher Degrees Committee

Appendix 3: Study Approval by the Research Committee of the Ministry of Health and Social Services

9 - 0/0001

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198 **Ministerial Building** **Tel: (061) 2032562**
Windhoek **Harvey Street** **Fax: (061) 272286**
Namibia **Windhoek** **E-mail: hilmanangombe@yahoo.com**

Enquiries: Ms. H. Nangombe Ref.: 17/3/3/AP **Date: 21 January 2010**

OFFICE OF THE PERMANENT SECRETARY

Mr. Evans. L. Sagwa
P. O. Box 90027
Klein Windhoek
Namibia

Dear Mr Sagwa,

RE: The prevalence and risk factors for occurrence of adverse effects of second line anti-tuberculosis medicines amongst patients on TB chemotherapy in a treatment facility in Namibia: 2009-10.

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. Kindly be informed that approval has been granted under the following conditions:

3.1 The data collected is only to be used for academic purpose;
3.2 A quarterly progress report is to be submitted to the Ministry's Research Unit;
3.3 Preliminary findings are to be submitted to the Ministry before the final report;
3.4 Final report to be submitted upon completion of the study;
3.5 Separate permission to be sought from the Ministry for the publication of the findings.

Yours sincerely,

MR. K. KAHUURE
PERMANENT SECRETARY

MINISTRY OF HEALTH AND SOCIAL SERVICES REPUBLIC OF NAMIBIA

"Health for All"

Appendix 4: Request for permission to collect data at the study facility

UNIVERSITY OF THE WESTERN CAPE

Private Bag X 17, Bellville 7535, South Africa
Tel: +27 21-959, Fax: 27 21-959
E-mail:

February 22, 2010

Evans .L. Sagwa
P O Box 90027
Klein Windhoek, Windhoek

The Principal Medical Officer
Walvis Bay State Hospital
Private Bag 5010, Walvis Bay.

Dear Sir,

Re: Request for permission to conduct a research study at the Kondja TB ward

This letter serves as a request to the management of the Walvis Bay State Hospital for permission to undertake a research study at Kondja TB ward. I am required to conduct this research in partial fulfilment of the requirements of the Master of Public Health Degree that I am studying at the University of the Western Cape, South Africa. The University of the Western Cape Higher Degrees Committee and the MoHSS research unit have reviewed and approved the technical and ethical aspects of this study (*please see attached the approval letters*).

The research will look into: ***The prevalence and risk factors for occurrence of adverse effects of second line anti-tuberculosis medicines amongst patients on TB chemotherapy in a treatment facility in Namibia: 2009-10***. Findings from the study will be shared with clinicians at the TB ward and the managers of the National TB Control Programme with a view of gaining an understanding of commonly encountered negative side-effects of second-line TB medicines that may be prevented through hospital or community-based approaches.

The study involves a cross-sectional, descriptive and analytic retrospective study design. The TB treatment records of all patients treated for drug-resistant TB at the study facility from 01 Jan 08 to the day of data collection will be reviewed. Data will be collected retrospectively from the patient TB treatment records using a structured data collection form.

I plan to visit the TB ward and conduct data collection from **Mon 01-March-2010** to **Fri 05-March-2010**. Kindly facilitate on-the-ground preparations for making available TB treatment records of patients treated with second-line TB medicines for the period **01-Jan-2008** to **28-Feb-2010**.

Yours Sincerely,

Mr Evans .L. Sagwa | Researcher -Telephone: + 264 (061) 22 80 16 | Cell: + 264 (0) 81 352 1030| Fax: + 264 (061) 220 361| Email: esagwa@msh.org.na

Appendix 5: Permission to collect data at the study facility

REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES
ERONGO REGION
WALVISBAY DISTRICT

Enquiries: Dr. J.P.I.Musasa

P/Bag: 5010 W/BAY
Tel : 064 – 216300
Fax: 064 – 216345
23rd February 2010

To: Mr. Evans. L. Sagwa
P.O.Box: 90027 Klein Windhoek
WINDHOEK/NAMIBIA

RE: Request for permission to conduct a research study at Kondja TB ward

Dear Sir,

The Walvis Bay District Coordinating Committee (DCC) acknowledges receipt of your dated 22.02.2010. After discussion, your research has been found of pertinent value.
The DCC of Walvis Bay Hospital has no objection and your request has bee approved.

Yours in Health

Dr. J.P.I. Musasa
Principal Medical Officer/Walvis Bay Hospital

MINISTRY OF HEALTH AND SOCIAL SERVICES
P/BAG 5010
23 FEB 2010
WALVIS BAY
WALVIS BAY HOSPITAL

Appendix 6: MDR-TB drug side effect monitoring form

Part A: Intensive phase DR-TB drug adverse effects monitoring form

Annex 18 No. 9-0/0031A

DRUG RESISTANT TUBERCULOSIS SIDE-EFFECT MONITORING FORM

INTENSIVE PHASE

Adverse effect (indicate grading *)	Week																								Management	Outcome
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
Abdominal pain																										
Constipation																										
Decreased																										
Depression																										
Diarrhea																										
Dizziness																										
Fatigue																										
Fever																										
Headache																										
Joint pain																										
Nausea																										
Psychosis																										
Rash																										
Skin dis-colouriza																										
Tiinitus																										
Tremors																										
Vision changes																										
Vomiting																										
Other (list)																										

* Grading: 1 = mild; requiring no intervention 2 = moderate; requiring palliative intervention 3 = severe; requiring change in treatment

Part B: Continuation phase DR-TB drug adverse effects monitoring form

DRUG RESISTANT TUBERCULOSIS SIDE-EFFECT MONITORING FORM

Continuation phase																					
Adverse effect (indicate grading*)	Month **																			Management	Outcome
Abdominal pain																					
Constipation																					
Decreased hearing																					
Depression																					
Diarrhea																					
Dizziness																					
Fatigue																					
Fever																					
Headache																					
Joint pain																					
Nausea																					
Psychosis																					
Rash																					
Skin dis-colourization																					
Tiinitus																					
Tremors																					
Vision changes																					
Vomiting																					
Other (list)																					

* Grading: 1 = mild; requiring no intervention 2 = moderate; requiring palliative intervention 3 = severe; requiring change in treatment

** Indicate in the first column the month of treatment that continuation phase started

Appendix 7: Abstract presented at the ICIUM conference, 2011

Abstract number 486

Prevalence and Risk Factors of Adverse Effects of Second-Line Anti-Tuberculous Medicines in a Treatment Facility in Namibia: 2009–10

Problem statement: Namibia reported 372 cases of DR-TB in 2009. Second-line TB medicines have more frequent and serious adverse effects (AEs). The high TB/HIV co-infection (58%) is a further complicating factor. With little documented information on the profile and risk factors of these AEs, managers of tuberculosis control programs, clinicians, and patients face challenges in optimizing treatment outcomes.

Objectives: To determine the types and frequency of AEs of second-line anti-TB medicines in a selected DR-TB treatment facility; to identify the AE risk factors

Design: Cross-sectional. Data were collected from patients' treatment records using a structured form. Descriptive statistics were applied to profile AEs. Logistic regression was used to calculate odds ratios [OR; 95% confidence interval (CI), $p < 0.05$] in risk factor analysis.

Setting: A district TB treatment facility

Study population: All patients treated for DR-TB at the study facility from January 2008 to February 2010

Outcome measure(s): Occurrence and characterization of AEs

Results: *Demographics:* Male (M) 64%; age (mean years ± SD), 36.9 ± 8.4 (M), 31 ± 10.2 (F); initial weight (mean kg ± SD), 53.6 ± 7.8 (M) and 49.8 ± 16.4 (F)

In total, 141 AEs were experienced in 90% (53/59) patients. Gastrointestinal tract (GIT) events were 64%, tinnitus 45%, joint pain 28%, and decreased hearing 25%. In 53% of patients, AEs resolved within 3 months. AEs were severe, requiring discontinuation of suspected medicine in 15% of patients, 9% recovering with sequelae.

Risk-factor analysis: Moderate-severe AEs were associated with HIV co-infection (OR 3.12; 95% CI 1.04–9.33, *p*= 0.04). AEs lasting >3 months were associated with ARV co-medication (OR 7.88; 95% CI 1.11–56.12, *p*=0.04). GIT effects were mostly experienced in the first month of DR-TB treatment (OR 4.29; 95% CI 1.25–14.73, *p*=0.02). Nausea was associated with AZT-based HAART (OR 7.50; 95% CI 1.09–51.51, *p*=0.04) and joint pain with the use of cycloserine-containing regimens (OR 6.35; 1.56–25.84, *p*=0.01). Risk of rash in females was OR 15.86; 95% CI 1.75–143.74, *p*=0.01. In 18 patients with mono/poly-resistant TB, low baseline body weight (≤45 kg) increased risk of GIT events (OR 16.50; 95% CI 1.10–250.2, *p*=0.04) and decreased hearing (OR 36.00; 95% CI 1.71–756, *p*=0.02). Risk of ototoxicity was highest in patients using amikacin (OR 12.00; 95% CI 1.29–111.32, *p*=0.03) and ciprofloxacin (OR 27; 95% CI 1.98–368.28, *p*=0.01). Among 37 MDR-TB patients, HIV co-infection increased risk of experiencing ≥3 AEs (OR 8.00; 95% CI 1.28–50.04, *p*=0.03), mostly moderate-severe AEs (OR 10.42; 95% CI 1.62–66.90, *p*=0.02). Joint pain occurred mostly in patients using cycloserine-based regimens (15.67; 95% CI 1.70–144.35, *p*= 0.02) and efavirenz-based HAART (OR 13.46; 95% CI 1.02–178.30, *p*=0.05).

Conclusions: Although AEs were highly prevalent in DR-TB chemotherapy, 85% of patients tolerated them. GIT effects and hearing loss were most common. Findings of risk-factor analysis are statistically imprecise, inconclusive, and require further study.