The incidence of linezolid-associated side effects in MDR/RR-TB patients receiving routine care at a tertiary hospital in Johannesburg, South Africa.

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Declaration

I, Nkateko Lebogang Ngolele declare that *the incidence of linezolid-associated side effects in MDR/RR-TB patients receiving routine care at a tertiary hospital in Johannesburg, South Africa* 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.

Nkateko Lebogang Ngolele

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Keywords

Linezolid

Adverse events

Drug resistant tuberculosis

South Africa

HIV co-infected

Optic neuropathy

Gastrointestinal toxicity

Peripheral neuropathy

Anaemia

Acronyms

TB	Tuberculosis
MDR -TB	Multi-drug resistant Tuberculosis
RR-TB	Rifampicin resistant Tuberculosis
XDR-TB	Extensively drug-resistant tuberculosis
WHO	World Health Organisation
HIV	Human Immunodeficiency Virus
AE	Adverse Event
TBPFIS	Tuberculosis focal point information system
TBFP	Tuberculosis focal point
HJH	Helen Joseph Hospital
DAIDS	Division of AIDS

Definitions of key concepts and terms

Gastrointestinal toxicity (GI-related) - includes nausea and vomiting, diarrhoea and abdominal pain (Boussios, Pentheroudakis, Katsanos, & Pavlidis, 2012).

Peripheral neuropathy - typically results in weakness, numbness, and discomfort, generally in the hands and feet, due to injury to peripheral nerves, which are nerves outside of the brain and spinal cord (Watson & Dyck, 2015).

Optic neuropathy - is when inflammation damages the optic nerve causing pain with eye movement and temporary vision loss.

Adverse event - an unanticipated medical issue that develops while receiving medication or other therapy treatment. Adverse reactions can range in severity from minor to severe. Also referred to as side effects.

Cured - refers to a patient who was smear- or culture-negative in the month before treatment ended (Guier & Stokkermans, 2022; WHO, 2013).

Completed - refers to a patient who completed treatment without showing signs of failure but who lacks documentation that sputum smear or culture results in the final month of treatment and on at least one prior occasion were negative, either because tests were not performed or because results are not available (WHO, 2013).

Lost to follow-up - refers to patients whose treatment has been stopped for 2 consecutive months or more (WHO, 2013).

Abstract

Background: Drug-resistant tuberculosis is currently considered an ongoing public health crisis and a health security threat. Several strategies for the management of MDR/RR- TB have been explored including the use of repurposed drugs like linezolid, fluoroquinolones, and the addition of new TB-specific medications like bedaquiline and delamanid. Linezolid has been extensively studied in the treatment of drug-resistant tuberculosis. Although linezolid is an important option for drug-resistant tuberculosis management, its prolonged use has been associated with treatment-limiting side effects including peripheral neuropathy, optic neuritis, myelosuppression including severe anaemia and gastrointestinal toxicity.

Aim: The aim of this study was to describe the incidence of linezolid-associated side effects in MDR/RR-TB patients receiving routine care at an outpatient treatment centre located in a tertiary-level hospital in Johannesburg.

Methods: This study was a retrospective medical file and record review. The study included records of patients who initiated MDR/RR-TB treatment at the TB focal point between May 2015 to February 2021. Two hundred and twenty-three (223) participants were chosen based on the inclusion criteria stipulated in the methodology chapter. Furthermore, 125 were excluded because of no documented linezolid prescription leaving 98 participants in the cohort.

Ethical considerations: Ethical approval was sought from the University of the Western Cape's Biomedical Research Ethics Committee as well as permission from Helen Joseph Hospital was sought and was also granted.

Results: Peripheral neuropathy and GI-Related adverse events were the most frequent adverse events reported. At least 21% of the cohort experienced side effects related to linezolid. The four most common side effects of linezolid in the population were anaemia, peripheral neuropathy, GI-related issues, and visual disturbances. The most common diagnosis, peripheral neuropathy, was found in 13% of patients, while the least common diagnosis, visual abnormalities, was found in 1% of patients.

Conclusion: Findings from this study demonstrates a lower incidence of linezolid-associated toxicity than has been previously described in the literature. This may be in part due to under-reporting or poor recording of side effects in the clinical record. However, in this study patients were able to complete the course of linezolid treatment without dose reduction or treatment interruptions. Although the findings are related to linezolid toxicity – note the possibility of the findings being influenced by other drugs. The study also had a lot of missing values which can be attributed to files missing information or the electronic files not being updated. Recommendations would be to emphasize on better documentation of adverse events in order for more research to be done in this area. A further recommendation would be conducting this type of study on a larger cohort in order to get more generalizable findings.

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Chapter One: Introduction

This chapter will introduce the study by first discussing the background and context of the research project, followed by the research problem, aims, objectives and research question, significance and finally the limitations that the project might face.

1.0 Introduction

Drug-resistant tuberculosis (DR-TB) is currently considered an ongoing public health crisis and a health security threat (Wasserman, Denti, Brust, Abdelwahab, Hlungulu, Wiesner, Norman, Sirgel, Warren, Esmail, Dheda, Gandhi, Meintjes & Maartens, 2019). In 2021, there were an estimated 450 000 new cases of rifampicin-resistant TB (RR-TB) (WHO, 2022). The case fatality rate of RR-TB is estimated at 40% which is higher than that of drug-sensitive tuberculosis which was 17% in 2019 (Osman, van Schalkwyk, Naidoo, Seddon, Dunbar, Dlamini, Welte, Hesseling, & Claassens, 2021; Wasserman et al, 2019). New and repurposed medications for the treatment of DR-TB have emerged in the past decade that offer improved outcomes, less toxicity and shorter treatment courses. One example of a repurposed medication is linezolid, which has been shown to improve treatment outcomes when used together with other DR-TB medications (Wasserman et al, 2019).

Although linezolid is highly effective, long-term use in DR-TB patients may be limited by its side effects. Prolonged use of linezolid has been associated with numerous side effects (Anger, Dworkin, Sharma, Munsiff, Nilsen & Ahuja, 2010) including peripheral neuropathy, myelosuppression including severe anaemia, gastrointestinal toxicity and optic neuropathy (Agyeman & Ofori-Asenso, 2016).

1.1 Background

Tuberculosis (TB) is caused by the bacterium *Mycobacterium tuberculosis* and is a significant contributor to global morbidity and mortality and prior to COVID-19 the single most common infectious cause of death (Agyeman & Ofori-Asenso, 2016; WHO Global TB Report, 2019). Furthermore, tuberculosis has attracted increased public health attention due to the alarming rates of multidrug-resistant (MDR) tuberculosis and extensively drug-resistant tuberculosis (XDR) (Zhang, Falagas, Vardakas, Wang, Qin, Wang & Liu, 2015).

Rifampicin-resistant (RR)-TB is tuberculosis caused by *Mycobacterium tuberculosis* strains that have developed resistance to the critical first-line TB drug rifampicin. MDR-TB is TB that is resistant to both rifampicin and isoniazid which is the second most important first-line drug for TB (Singh, Cocker, Ryan & Sloan, 2019). In 2021, the World Health Organisation estimated that the burden of DR-TB had increased by 3% between 2020 - 2021 to 450 000 (399 000–501 000) new RR-TB patients (WHO, 2022). Only one-third of the people reported starting treatment in 2021 and the current treatment success rate is at 60% globally (WHO, 2022).

South Africa had a total incidence of TB at 304 000 (207 000-421 000) in 2021. In 2021, MDR TB/RR TB had an incidence of 21 000 (13 000-29 000), with a treatment coverage of 57% and a case-fatality ratio of 19% in 2021 (WHO, 2022).

Several strategies for the management of MDR/RR- TB have been explored including the use of repurposed drugs like linezolid, fluoroquinolones, and the addition of new TB-specific medications like bedaquiline and delamanid (Prasad, Gupta & Banka, 2018). The World Health Organization (WHO) recommended the use of linezolid as a preferred agent for all patients with MDR/RR-TB in 2018 (Wasserman et al., 2019). In the updated MDR/RR-TB treatment guidelines

in 2020, the WHO ranked MDR/RR medications based on their relative effectiveness (WHO, 2020). The medications that are considered most effective are classified as 'Group A' drugs and include fluoroquinolones (i.e. levofloxacin or moxifloxacin), bedaquiline, and linezolid (which are all oral medications) (World Health Organization, 2020). Injectable aminoglycosides, which were previously routinely used in the treatment of RR/MDR but were highly toxic due to high rates of hearing loss and vestibular toxicity, were downgraded to 'Group C' where they should be included only if there are no better options available for treatment (World Health Organization, 2020).

Linezolid has been extensively studied in the treatment of drug-resistant tuberculosis. In a meta-analysis conducted in 2019, it was found that linezolid use increased the treatment success odds by 3-fold and significantly lowered the mortality rate (adjusted risk difference –0·20, 95% Confidence Interval –0·23 to –0·16) (Singh, Cocker, Ryan & Sloan, 2019).

Although linezolid is an important option for drug-resistant tuberculosis management, its prolonged use has been associated with treatment-limiting side effects (Anger et al.,2010) including peripheral neuropathy, optic neuritis, myelosuppression including severe anaemia, and gastrointestinal toxicity (Agyeman & Ofori-Asenso, 2016). Linezolid-associated side effects are common and affect over 80% of the participants in some studies (Singh, Cocker, Ryan & Sloan, 2019).

As linezolid has been rolled out for wider use, a closer look at the adverse events data is needed to understand the effects in different populations including people with HIV and in low-resource settings where close monitoring of treatment side effects may be limited (Singh, Cocker, Ryan, & Sloan, 2019). Analyses done to date suggest that linezolid-associated side effects are increased in patients with HIV (Wasserman et al., 2019). This suggests linezolid toxicity may be increased among HIV-positive patients (Wasserman et al, 2019).

Linezolid was implemented as a group A drug in South Africa for the treatment of MDR/RR-TB in 2018, however, it is not known if treatment-related side effects have limited its use (Bolhuis, Akkerman, Sturkenboom, Ghimire, Srivastava, Gumbo &Alffenaar, 2018; National Department of Health, 2019).

The pharmacokinetics (PK) for the optimal dosing of linezolid dosing are poorly defined in patients with TB in Sub-Saharan Africa, where there is a high burden of HIV coinfection (Wasserman et al., 2019). Understanding the PK is important to apply the population-specific factors that may influence drug disposition and drug effects (Wasserman et al., 2019).

1.2 Research problem

Linezolid toxicity is a major concern for medical professionals and often limits the dose and duration of treatment with the drug. A systematic review published in 2015 found that at least 31% of patients with DR-TB receiving linezolid experienced anaemia and 27% had peripheral neuropathy (Hughes, Isaakidis, Andries, Mansoor, Cox, Meintjes & Cox, 2015). There has not been any research done in outpatient settings in South Africa. However, what should be noted is that there have been some clinical trials done in South Africa namely, the Nix trial and the Ze-nix trial which both recorded linezolid-related toxicity in the patients.

More research is required to understand the burden and impact of linezolid-associated side effects in MDR/RR-TB patients under routine care settings with high rates of HIV coinfection.

1.3 Research Purpose

This research aims to describe the incidence of linezolid-associated side effects in patients with multi-drug resistant and/or rifampicin-resistant TB (MDR/RR-TB) receiving outpatient DR-TB treatment in a tertiary-level academic hospital in Johannesburg.

This study will contribute to the knowledge of linezolid-related toxicity in routine care conditions. A clearer understanding of the dosing and adverse events may inform policy decisions around the use of linezolid. This will also help address the current shortage of research in this area (in nonclinical environments) and will provide preliminary data.

1.4 Research question

What is the incidence of linezolid-associated side effects in people receiving MDR/RR-TB routine outpatient care at a tertiary-level referral hospital in Johannesburg, South Africa?

1.5 Research setting

The study was conducted at the TB Focal Point (TBFP) clinic located at Helen Joseph Hospital is an outpatient DR-TB treatment facility in the City of Johannesburg (COJ), the largest metropolitan area in the country with an estimated population of 4.4 million in 2011 (Statistics South Africa, 2011). Helen Joseph Hospital is a tertiary care facility and a teaching hospital at the University of Witwatersrand. The TBFP was established in 2008 and provides routine TB diagnosis for inpatients and outpatients, treatment for patients with drug-resistant TB, complications of TB treatment and non-tuberculous mycobacterial infections (Voss De Lima, 2013). During the study period, the TBFP treated approximately 100 new MDR/RR-TB cases every year. The TBFP is located adjacent to Themba Lethu Clinic, an outpatient HIV treatment facility that offers routine HIV care and treatment for thousands of patients every year. Themba Lethu used to be the largest antiretroviral therapy (ART) site in South Africa (Fox , Maskew, MacPhail, Long, Brennan, Westreich, MacLeod, Majuba & Sanne, 2012) prior to the decentralization of ART to primary health care clinics. The TBFP is staffed by 1 senior and 1 junior medical officer and a team of

nursing staff and counsellors. Approximately 500 patients have been initiated on linezolid-containing MDR/RR-TB treatment regimens at the TBFP between 2015 to 2021.

1.6 Research Aims

Given the lack of research regarding the incidence of linezolid toxicity in sub–Saharan Africa under routine care conditions this research will aim to describe the incidence of linezolid-associated side effects in MDR/RR-TB patients receiving routine care at an outpatient treatment centre located in a tertiary level hospital in Johannesburg.

1.7 Objectives

1. To describe the baseline characteristics of the patients enrolling for treatment and care of MDR/RR-TB at the TB Focal Point.
2. To describe the incidence of linezolid side effects defined as peripheral neuropathy, optic neuropathy, myelosuppression, and gastrointestinal toxicity in patients receiving care DR-TB.
3. To describe the severity of linezolid-associated side effects in patients receiving DR-TB care
4. To compare the incidence of linezolid-associated side effects in HIV co-infected vs HIV-negative populations.

1.8 Conclusion

In this chapter the context of the study has been introduced. The research objectives and the problem have been identified and the value of this research has been stated, including the research setting.

In chapter two the existing literature will be reviewed to determine the incidence of linezolid-associated side effects, the major reported side effects of linezolid and the clinical management of these adverse events. In chapter three the theoretical framework will be presented. The adoption of a quantitative research approach will be justified, and the broader research design will be discussed including the limitations. Chapter four will present the findings of this research. Chapter five will include a discussion of the findings. Chapter six will conclude the study with recommendations and limitations.

Chapter Two: Literature Review

2.0 Introduction

This chapter reviews and synthesises the existing literature in relation to the study's aim and objectives. It will focus on determining the incidence of linezolid-associated side effects, describing the major reported side effects of linezolid and the clinical management of these adverse events according to the literature.

2.1 Incidence of linezolid-associated side effects

In 2015 a systematic review was published that summarised data from fifteen studies (eleven were retrospective studies, three were prospective studies and one randomised control trial) and found that there was a 35% incidence of major adverse events that required discontinuation or dose reduction of linezolid (Zhang et al., 2015). Moreover, what should be highlighted is that none of the studies included in the review were from Sub-Saharan Africa where there is high rates of HIV coinfection and limited monitoring capability which may increase the risk of linezolid toxicity (Wasserman et al., 2022). 47% of the studies were conducted in Asia and 33% in Europe. 9% of the patients included in the systematic review had HIV co-infection and 46% of the cases included had XDR-TB (Zhang et al., 2015).

In the systematic review conducted by Zhang et al. (2015) they found 54% of patients experienced adverse events presumably linked to linezolid. Peripheral neuropathy was found in 31% of the patients included in the review, anaemia in 27% and optic neuritis in 8%. Moreover, they found that patients that received lower linezolid doses – received treatment for longer than those who received a higher dosage of linezolid (Zhang et al., 2015).

Zhang et al further suggest that the incidence of myelosuppression appears to be dose-related while peripheral and optic neuropathy were more treatment duration-dependent. In a randomized trial of linezolid in XDR TB patients in South Korea who had failed treatment published in 2012 (Lee Lee, Carroll, Choi, Min, Song, Via, Goldfeder, Kang, Jin, Park, Kwak, Kim, Jeon, Jeong, Joh, Chen, Olivier, Shaw & Barry, 2012), linezolid was administered at a dose of 600 mg daily for four months and 300 mg daily for 18 months. Anaemia developed during the first four months of therapy when patients were receiving the higher dose of 600 mg daily while neuropathy developed after the fifth month when most patients were receiving 300 mg daily (Lee at al 2012; Zhang et al., 2015). This dose-related toxicity was also described by Abdelwahab et al. (2021) who also found that a 600 mg daily dose had a 54% probability of exceeding the toxicity trough threshold (Abdelwahab, Wasserman, Brust, Dheda, Wiesner, Gandhi, Warren, Sirge, Meintjes, Maartens, & Denti, 2021).

In the Nix-TB trial, Conradie et al (2020) completed an open-label clinical trial enrolling XDR TB patients and MDR TB patients who were no longer responding to the second-line regimen or were discontinued because of adverse events. In addition to receiving bedaquiline and pretomanid, the participant's treatment included linezolid 1200 mg daily dropped to 600 mg daily in the event of toxicity. 51% of the trial's participants were HIV positive. All the participants had at least one adverse event recorded. 81% experienced peripheral neuropathy and myelosuppression in 48% of the participants. The Nix-TB Trial had great treatment outcomes with linezolid-containing treatment with 90% of the participants having favourable outcomes (Conradie, Diacon, Ngubane, Howell, Everitt, Crook, Mendel, Egizi, Moreira, Timm, McHugh, Wills, Bateson, Hunt, van Niekerk, Li, Olugbosi, & Spigelman, 2020).

In a prospective observational cohort study of one hundred and fifty-one patients with MDR/RR-TB in South Africa. Wasserman, Brust, Abdelwahab, Little, Denti, Wiesner, Gandhi, Meintjes, & Maartens (2022) found the incidence of anaemia was 39% and peripheral neuropathy was 20%. In a prospective randomized clinical trial of linezolid in XDR patients in China, Tang, Yao, Hao, Zhang, Liu, Liu, Wu, Zen, Sun, Liu & Gu (2015) found that 81.8% of the patients on linezolid therapy had clinically significant adverse events and 93% of the events were possibly related to linezolid therapy (Tang et al., 2015). Zhang et al., (2015) identified approximately 50% of adverse events due to linezolid in a systematic and meta-analysis review.

Conradie, Bagdasaryan, Borisov, Howell, Mikiashvili, Ngubane, Samoilova, Skornykova, Tudor, Variava, Yablonskiy, Everitt, Wills, Sun, Olugbosi, Egizi, Li, Holsta, Timm, Spigelman (2022) conducted a randomized trial (Ze-Nix) with four different linezolid dosing and duration strategies in XDR TB patients and pre -XDR TB patients in South Africa comparing participants receiving a regimen including linezolid at 1200mg for 26 weeks vs 1200mg for 9 weeks vs 600mg for 26 weeks vs 600mg for 9 weeks. At least one adverse event was reported in 86% of the participants. In the lower dose (600mg) groups there were lower rates of peripheral neuropathy (26 weeks had 24% vs 9 weeks had 13%), compared to the higher dose group (1200mg) (26 weeks had 38% vs 9 weeks had 24%). Myelosuppression was higher in the higher dose groups (26 weeks had 22% vs 9 weeks had 15%) compared to the lower dose group which had (26 weeks had 2% vs 9 weeks had 7%). The trial found that 90% of their participants had a favourable outcome - 1200mg for 26 weeks producing 93% of a favourable treatment outcome in its cohort. The 600mg dose for 26 weeks was considered to be the most effective and favourable dosing strategy among the four strategies and forms the basis of the updated DR-TB treatment guidance issued by the WHO in 2022. Therefore, the WHO issued rapid communication whereby they endorsed the 6 months all

oral medication used in the Nix and Ze-Nix trials which included bedaquiline, pretomanid and linezolid (WHO, 2022).

Anaemia followed by mild peripheral neuropathy was the most common adverse event reported by multiple tuberculosis studies (Wasserman et al., 2022). Wasserman et al. (2022) found that the most adverse events occurred within the first four months of linezolid-containing treatment. Furthermore, they found that the onset of anaemia and peripheral neuropathy was similar both starting approximately at week ten of treatment. However, neuropathy occurred later than myelosuppression in other studies which would imply a duration-dependent effect for neurotoxicity furthermore, these studies had multiple limitations which include being too small and lacked consistent outcome definitions and there was not enough biological evidence or explanation for that hypothesis (Wasserman et al., 2022).

In previous research conducted in other settings, myelosuppression was found to occur in approximately 30% of the study population, peripheral neuropathy in 30% of the patients within 2 – 4 months, and optic neuropathy occurs after 5 -10 months of treatment in approximately 30% of patients (Jaspard, Butel, El Helali, Marigot-Outtandy, Guillot, Peytavin, &- Pourcher, 2020). Zhang et al. (2015) found that peripheral neuropathy and anaemia constituted the main identified adverse events and with gastrointestinal disorders, optic neuritis, thrombocytopenia and leukopenia being less common.

Tang et al. (2015) conducted a prospective, multicentre, randomised study to evaluate the efficacy, safety and tolerability of linezolid in patients in China. Sixty-five (65) patients who had culture-positive sputum for XDR-TB were randomly assigned to a linezolid therapy group or a control group (Tang et al., 2015). Approximately 51% of the patients developed anaemia, 48% developed nausea/vomiting, 24% developed optic neuropathy and 18% developed peripheral neuropathy

which was higher than in the control group ($p<0.05$) (Tang et al., 2015). Tang et al. (2015) also found that haematological adverse reactions that include anaemia occurred between 2 weeks and 2 months after starting linezolid treatment (Tang et al., 2015).

Gastrointestinal adverse reactions that included nausea or vomiting occurred between 2 weeks and 4 weeks (Tang et al., 2015). They additionally observed that peripheral neuropathy occurred between 2 months and 4 months, while optic neuropathy occurred later around 5–6 months (Tang et al., 2015).

2.2 Mechanisms of action and pathophysiology of linezolid toxicity

Linezolid belongs to a class of medications called 'oxazolidinones' that inhibit protein synthesis in the bacterial ribosome (Singh, Cocker, Ryan & Sloan, 2019). Linezolid binds to the homologous structure at the *M. tuberculosis* site essentially causing toxicity that is dose related manifesting as neuropathy and myelosuppression (Wasserman et al., 2022).

The linezolid mechanisms are currently not well understood. Protein synthesis in the mitochondria may be impacted by linezolid or it may have an immediate toxic effect on nerve cells, resulting in optic neuritis and peripheral neuropathy (Rucker, Hamilton, Bardenstein, Isada & Lee, 2006).

The hands and feet are often affected by peripheral neuropathy, which typically manifests as "glove and stocking" distribution. Reduced vision and changes in colour perception are two symptoms of optic neuritis (Rucker, Hamilton, Bardenstein, Isada & Lee, 2006).

2.3 Clinical management of adverse events

Lifan, Sainan, Feng, Siyan & Xiaoqing (2019) found that ten studies reported reductions in dosage or discontinuation of linezolid due to adverse events which included anaemia, peripheral

neuropathy, optic neuropathy and nausea. The literature suggests that the adverse effects were reversible after the dose reduction. Most events are resolved after the reduction or discontinuation of linezolid therapy (Tang et al., 2015). Lifan, Sainan, Feng, Siyan & Xiaoqing (2019) found that the treatment success rates of linezolid therapy in patients with XDR-TB were high although they found that the adverse effects were very common.

A review conducted by Singh et al (Singh, Cocker, Ryan & Sloan, 2019), looked at three countries namely the Republic of Korea, South Africa and China. They found that there were higher rates of adverse event cases among participants in the linezolid group than among controls (Singh, Cocker, Ryan & Sloan, 2019). However, they noted that they could not reliably compare the total adverse events, serious adverse events, and overall and specific linezolid-associated adverse events due to a lack of data on follow-up duration and numbers of participants experiencing linezolid-associated adverse events (Singh, Cocker, Ryan & Sloan, 2019).

Wasserman et al. (2019) emphasized that linezolid dosage showed the need for adverse event monitoring with linezolid therapy even after the dose was reduced (Wasserman et al., 2019). Conradie et al. (2020) found that patients taking linezolid therapy should be monitored carefully (Conradie et al., 2020).

Wasserman et al. (2021) highlighted the need for toxicity monitoring once again. And found that there was no impact of HIV infection on linezolid toxicity, although two smaller studies had suggested that HIV may have been a possible risk factor for linezolid-associated adverse events, and if the association is rea; then it is probably driven by the pharmacodynamic effects in HIV (Wasserman et al., 2021).

Close clinical monitoring for adverse events of linezolid treatment is of critical importance (Abdelwahab et al. 2021). In the updated 2020 DR-TB treatment guidelines, the WHO highlights the importance of National TB Programmes implementing active TB drug safety and monitoring management strategies for all patients receiving DR-TB treatment (WHO DR-TB guidelines 2020). The South African guidelines on DR-TB management specify that patients should undergo monthly monitoring for toxicity including full blood count with differential, visual acuity testing and screening for peripheral neuropathy for the duration of linezolid treatment (Management of rifampicin-resistant tuberculosis: a clinical reference guide, National Department of Health, 2019).

Chapter Three: Methodology

3.0 Introduction

In this chapter the methodology will be described, and the following will be outlined, the study design, research setting, and study population. It will continue with sampling, data collection, data analysis, rigour, and finally ethical considerations.

3.1 Study Design

This study was a retrospective medical record review. This study used a quantitative retrospective cohort design to measure the incidence of linezolid toxicity within the population of patients initiated on MDR/RR-TB (Setia, 2016; Thiese, 2014). The study included records of patients who initiated MDR/RR-TB treatment at the TB focal point between May 2015 to February 2021.

This study design was used as it looked back at archived data that would be readily available and it would be inexpensive to perform. However, what should be noted is the poor control over the confounders, missing information and

3.2 Study population

The study population was all the patients at the study site that received routine MDR/RR-TB treatment that included linezolid. The indications of treatment varied during the study period: between May 2015 and June 2018 linezolid and bedaquiline were used in patients who had a treatment-limiting side effect or a contraindication to aminoglycoside therapy. In June 2018, the South African National Department of Health adopted an all-oral regimen for the treatment of RR/MDR and linezolid was given to all patients initiating treatment who did not have a contra-indication (National Department of Health, 2018).

Since June 2018, the following two oral regimens have been in use for the treatment of MDR/RR-TB in South Africa (National Department of Health, 2018)

- Short course (9-11 months of treatment) –Which includes bedaquiline (6 months), linezolid (2 months), clofazimine, high dose isoniazid, levofloxacin, pyrazinamide and ethambutol during the intensive phase.
- Long course (20 months of treatment) – This includes bedaquiline (6 months), linezolid (6 months), clofazimine, terizidone, pyrazinamide and high-dose isoniazid or ethionamide during the intensive phase.

In order to assess the final treatment outcome for all the patients in the sample, the review was limited to patients who initiated treatment no later than 30 May 2020 for the long course and 28 February 2021 for short-course treatment.

3.3 Sampling

Purposive sampling was used to select the participants who were eligible according to the study eligibility criteria. The sample was accessed from the Tuberculosis Focal Point Information System (TBFP-FIS) database that is used at the tertiary hospital.

The sample size was calculated using Epitools (epidemiological calculators) (Sergeant, 2018), where n = (Z2 x P x (1 - P))/e2 (Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI), P is expected true proportion, e is desired precision (half desired CI width)). Using a study population size of approximately 500 patients with a confidence level of 95%, a 5% margin of error and a proportion of 50% the ideal sample size was 218 patient files to accurately determine the incidence of linezolid-associated side effects.

3.3.1 Study inclusion criteria

- Patients over 18 years of age at the time of enrolling for care at the TBFP.
- Enrolled for care (medical record opened, seen by clinic staff) at the TBFP before 28 February 2021.
- Patient medical records are available for review on-site.
- Have documentation of any rifampicin-resistant drug resistance pattern, including mono resistance to rifampicin, poly-resistance including rifampicin, MDR-TB and pre-XDR TB.

3.3.2 Study exclusion criteria

- Patients under 18 years of age at the time of enrolling for care at the TB Focal Point.
- Resistance to bedaquiline or linezolid at baseline

3.3.3 Study participants

The researcher included 223 participants out of the 571 enrolled in the adverse event study. The 223 participants were chosen based on the inclusion criteria stipulated in the methodology chapter. Furthermore, 125 were excluded because of no documented linezolid prescription leaving 98 participants in the cohort (shown in figure 1).

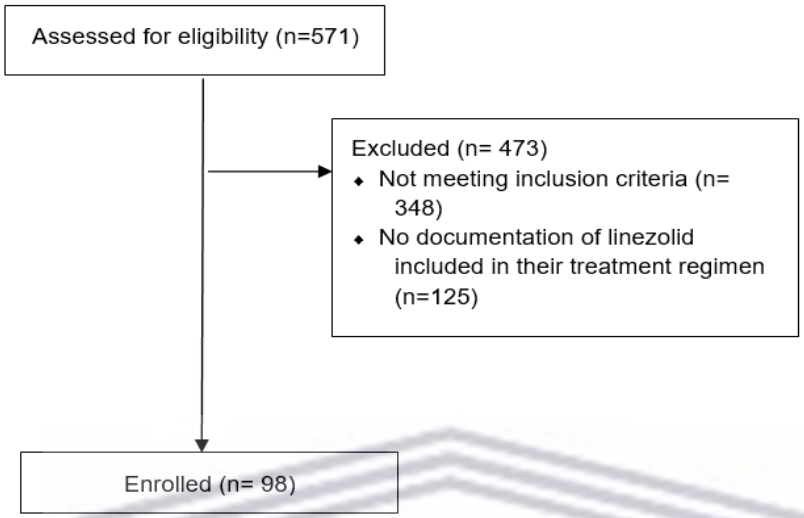

Figure 1: Flow diagram for sample inclusion

3.4 Data Collection

Patient medical records for the TB Focal Point are typically maintained as paper and electronic files and are stored separately. Medical records in this case are defined as the information that is routinely captured by the site's clinical staff for the management of patients which is paper files, then the electronic versions are usually used for patient scheduling and have general data.

The researcher trained medical students from the University of the Witwatersrand on how to do a file review to collect data for an ongoing study of adverse events among patients with DR-TB treated at TBFP. Training occurred once virtually and twice in person during which they were instructed on how to find the files and where to look for additional information if it is not found in one part of the TB stationery (as it has changed a few times over the years). The researcher supervised and oversaw the data collection process. And the researcher was available for any questions or assistance needed.

Both paper and electronic records were reviewed. Patients eligible were identified using the Tuberculosis Focal Point Information System (TBFPFIS). A data collection instrument was generated on RedCap using the data extraction tool and field workers who were medical students at the University of the Witwatersrand collected the study data and were supervised by the researcher of this study. The data was collected using RedCap.

Records that were eligible were assigned random study IDs once their files were identified. Adverse events and clinical management information regarding the adverse events were extracted from medical records (hard copy). Other information that was collected included demographics (age & gender), HIV status, treatment start date and treatment outcomes that were extracted from TB FIS (electronic).

The data that was collected was reviewed for completeness and consistency by the researcher. The researcher then extracted data from the data set that was collected – and looked at only eligible participants. A total number of 571 files were reviewed by the research assistants for the study of the adverse events and the researcher used 223 files that fulfilled the study enrolment criteria.

3.5 Outcome Definitions

Linezolid toxicity measured by anaemia, gastrointestinal toxicity, peripheral and optic neuropathy graded according to Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events; Version 2.1.

GI-related adverse events were graded 1 (mild) if they were for short periods of time and had little to no interference with their intake of oral medication. Grade 2 (moderate) would be persistent episodes between 24 -48 hours of either of the symptoms listed above causing mild dehydration and decreased oral intake of their medication. Grade 3 would be persistent episodes

for more than 48 hours with rehydration via IV fluids required. Grade 4 would be hypotensive shock (Boussios, Pentheroudakis, Katsanos & Pavlidis, 2012).

Peripheral neuropathy was graded as 1 if it was minor muscle weakness that has little to no impact on daily functional activities. Grade 2 would be muscle weakness causing more than minimal interference in functional activities. Grade 3 would be muscle weakness causing an inability to do functional activities. Grade 4 would be disabling respiratory muscle or muscle weakness (Watson & Dyck, 2015).

Optic neuropathy was graded as 1 if there were visual changes that have little or no interference with daily functional activities. Grade 2 would be visual changes causing more than minimal interference in functional activities. Grade 3 would be visual changes causing an inability to do functional activities. Grade 4 would be disabling visual loss.

3.6 Data Analysis

The data was cleaned and checked for errors and outliers, in excel and then imported into STATA version 13. The study analysed the proportion of patients receiving linezolid therapy and the proportion of patients who develop adverse events.

The primary outcome measure was the proportion of patients who developed one of the following side effects from linezolid: peripheral neuropathy, optic neuropathy, myelosuppression, or gastrointestinal toxicity.

The secondary measure was the incidence of adverse events that developed in HIV-negative patients vs HIV-positive patients.

Tertiary outcome measures were the incidence and severity of linezolid-associated side effects in HIV co-infected vs HIV-negative populations. The proportion of HIV-positive and negative patients who experienced linezolid-associated side effects and the severity of the side effects. A risk-ratio was performed to compare adverse events in patients who are HIV-positive and those that are HIV negative.

Another risk ratio was performed to compare adverse events in males and females

The analysis also consisted of frequencies, means, medians, risk ratios of the incidence of linezolid-associated side effects and the severity of the side effects.

3.6 Rigor

Prior to beginning the research, the researcher sampled 5% of the files. This was used to train the research assistants and to help identify any concerns with the availability rates of the files, completion and accuracy rates of the files.

Inconsistent and incorrect adverse event grading can lead to incorrect interpretation of data and inaccurate data analysis. Adverse severity outcomes were graded as per the Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events (DAIDS Table for Grading the Severity of Adult and Paediatric Adverse Events in order to ensure and maintain accuracy and consistency in the evaluation of adverse events (US Department of Health and Human Services National Institutes of Health, National Institute of Allergy and Infectious Diseases & Division of AIDS, 2017). The DAIDS grading table provides severity grading scores that include grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (potentially life-threatening and/or requiring hospitalization) and lastly grade 5 (death) for all potential treatment-related toxicities.

The research assistants used the Division of AIDs table to grade adverse events if there was enough information to grade it and those without enough information were recorded as no severity recorded.

In previous research assessing linezolid pharmacokinetics of MDR TB treatment, using DAIDS, adverse events were assessed for attribution to linezolid based on the judgment of the investigator, who was not blinded to the presence or duration of linezolid treatment, and graded for severity (Garcia-Prats, Schaaf, Draper, Garcia-Cremades, Winckler, Wiesner, Hesseling & Savic, 2019) thus validating the use.

3.7 Ethical Considerations

Ethical approval was sought from the University of the Western Cape's Biomedical Research Ethics Committee and once granted permission from Helen Joseph Hospital was also granted.

The study posed minimal risk to participants as it used secondary data and there was no interaction with patients and no identifying information was collected and retained. Records were captured into the study database which is password protected on a password-protected laptop. Records that were eligible were assigned a random study ID number; patient identifiers were not entered into the study dataset. Access to the information was limited to the researcher and all data will be stored in password-protected files for five years, and after five years the files will be destroyed.

3.8 COVID-19 Considerations

- Data collection happened at less busy times including after-hours/weekends when TBFP is quiet to minimize the risk.

- The research assistants followed the recommendations from the local ethics committee and the Department of Health on when it is safe to be operational in the field.
- The researcher ensured that the research assistants had access to the necessary Personal Protective Equipment (PPE) (e.g., hand sanitiser, masks, and shields) and practice social distancing.

Chapter Four: Results

4.0 Introduction

This chapter presents the findings of the study. The results in this section consist of the characteristics of patients presenting for care, the description of the incidence of linezolid side effects, the severity of the side effects, a comparison of the incidence of linezolid-associated side effects in HIV co-infected vs HIV negative population, and a comparison of treatment outcomes of patients with and without premature discontinuation of linezolid therapy at the TB Focal Point.

4.1 Baseline characteristics of the study patients' records

The baseline characteristics of the cohort of patient records, which fit the eligibility criteria of this study, are shown in Table 1. Seventy-five (76.5%) were HIV positive and 21(29%) had a prior history of TB treatment failure or had been lost to follow-up from TB treatment. Thirty-nine (39) (39.7%) were female and there was a mean age of the cohort on linezolid was 37. There was a higher percentage of men in the linezolid group (59, 60.3%). Sixty-two point two percent (62.2 % of patients) treated with linezolid had no prior history.

Variable	Linezolid patients (n= 98)
Age – mean (Interquartile range (IQR))	37 (24-56)
Gender % (n)	
Male	60.3 (59)
Female	39.7 (39)
HIV Status % (n)	
Positive	76.5 (75)
Negative	21.4 (21)
Missing (Unknown)	2.1 (2)
Baseline HB – mean (IQR)	11.6 (10.2-13.3)
Missing (Unknown)	57
Baseline CD4 cells/mm3 – mean (IQR)	145 (33-164)
Missing (n)	44
TB Category % (n)	
New	62.2 (61)
Relapse/Lost to follow-up	29.5 (29)
Unknown	8.1 (8)

Table 1: Baseline Characteristics

4.2 Linezolid associated side effects

Out of the cohort of 98 patients who received linezolid, 21 (21.4%) participants experienced adverse events associated with linezolid (as shown in figure 2).

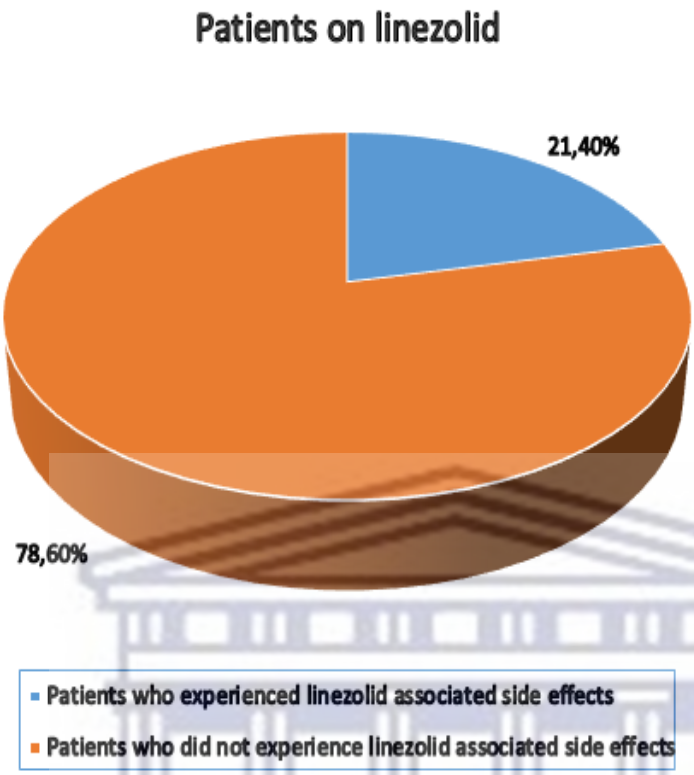

Figure 2: Patients on linezolid

The incidence of the adverse events of interest (anaemia, peripheral neuropathy, GI related toxicity, optic neuritis) was tabulated in Table 2. Peripheral neuropathy had the highest number of patients who experienced it at 13 (13.2%) and the lowest being visual disturbances which stands at 1%.

Adverse event (AE)	**Number of participants who experienced AE of interest** n (%)
Anaemia	4 (4.1)
Peripheral neuropathy	13 (13.2)
GI side effects	11 (11.2)
Visual disturbances (possible optic neuritis)	1 (1)

Table 2: Incidence of linezolid associated AEs

4.3 HIV Status of patients who experienced linezolid associated adverse events

Fourteen of the 21 patients (66.7%) with adverse events were HIV positive and 6 (28.6%) were HIV negative as illustrated in figure 3.

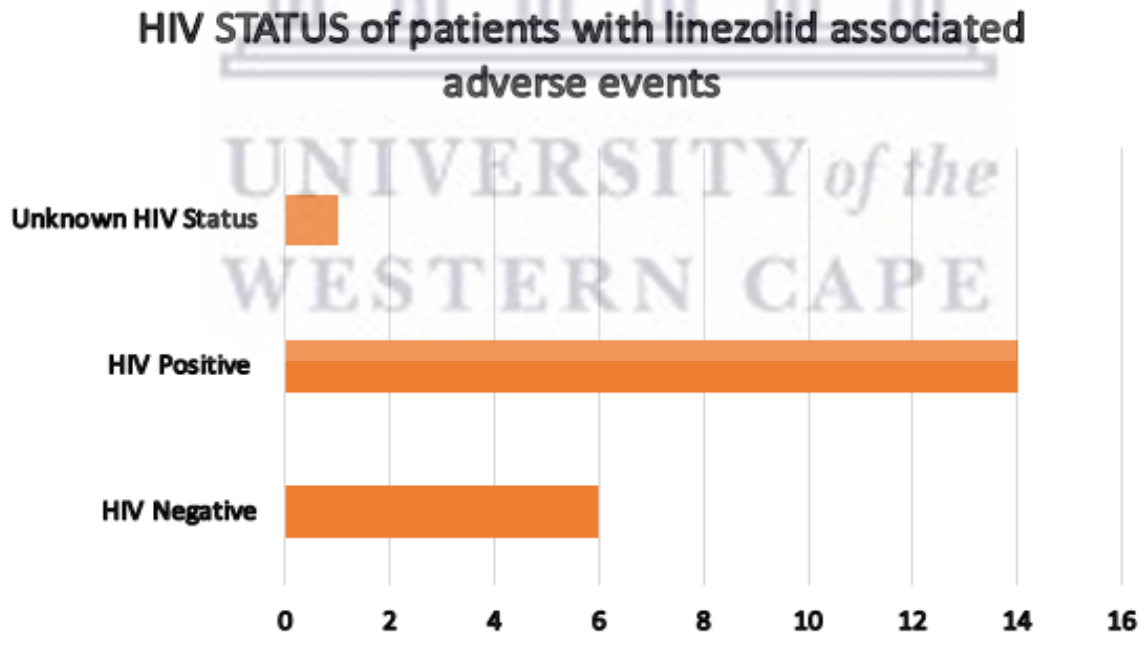

Figure 3: Number of HIV+/- patients with linezolid associated side effects

4.4 Risk ratio of adverse events

Table 3 further compares the incidence of linezolid-associated side effects in HIV co-infected vs HIV-negative patients. There were no statistically significant differences in the rates of linezolid associated anaemia, neuropathy, GI related side effects or visual disturbances between people with and without HIV co-infection.

Variable	**HIV positive** n=75 n (%)	**HIV negative** n=21 n (%)	**Risk ratio (95% CI)**
Anaemia	2/75 (2.7%)	2 /21 (9.5%)	0.28 (0.04-1.87)
Neuropathy	10/75 (13.3%)	3 /21 (14.3%)	0.93 (0.28 3.07)
GI side effects	6 /75 (8.0%)	4 /21 (19.1%)	0.42 (0.13 - 1.35)
Visual disturbances	0	1 /21 (4.7%)	0.09 (0.004 – 2.286)

Table 3: Incidence and relative risk of adverse events in people with and without HIV infection

Table 4 further compares the incidence of linezolid-associated side effects in males vs females The results also shows that there was no association with regards to gender and the risk of adverse events.

Variable	**Male** n=59 n (%)	**Female** n=39 n (%)	**Risk ratio (95% CI)**
Anaemia	0/59 (0)	4/39(10.3%)	0.07 (0.0041 - 1.34)
Neuropathy	12/59 (20.3%)	1/39 (2.6%)	7.93 (1.07 - 58.58)
GI side effects	5 /59 (8.7%)	6/39 (15.8%)	0.55 (0.18 -1.68)
Visual disturbances	0	1 /39 (2.6%)	0.22 (0.01 to 5.32)

Table 4: Incidence and relative risk of adverse events in males and females

4.5 Severity of adverse events

Table 5 below goes on to further break down the different adverse events by severity using the DAIDS grading scores ranging from mild (grade 1), moderate (grade 2), severe (grade 3), potentially life-threatening and/or requiring hospitalization (grade 4) and lastly death (grade 5) (US Department of Health and Human Services National Institutes of Health, National Institute of Allergy and Infectious Diseases & Division of AIDS, 2017). No grade 4 or 5 linezolid related adverse events were reported in this study. The most reported adverse event was peripheral neuropathy which occurred in 13 patients, most of which were graded as mild (n=6) (grade 1), 1 was graded at grade 2 (moderate) and 2 were graded at severe (grade 3), however, 4 patients could not be graded. The second most common adverse event, GI side effects, occurred in 11 patients, and again most cases 8 were graded as mild and only 1 was grade 2 (moderate). Anaemia was a rare event occurring in 4 patients, and 1 of the cases was graded as grade 1 (mild), 1 as grade 2 (moderate), 1 as grade 3 (severe) and 1 was not graded. And the lowest reported adverse event was visual disturbances which were only reported once and was graded at grade 1.

Adverse Event	**Number of times AE reported** (n=98)(%)	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Severity not recorded**
Anaemia n(%)	4 (4.1)	1	1	1	1
Peripheral Neuropathy n(%)	13 (13.2)	6	1	2	4
GI-Related n(%)	11 (11)	8	1	-	2
Visual Disturbances n(%)	1(1)	1	-	-	-

Table 5: Grading of the severity of linezolid associated side effects using the DAIDS

4.5 Treatment outcomes of patients

There was no premature discontinuation of linezolid therapy and no dose reduction in the current cohort and as a result it was not possible compare outcomes of patients who had linezolid discontinued vs those who completed the intended course. However, the treatment outcomes have been tabulated in the table below. The final treatment outcome was missing in 20/98 (20.4%); 53/98 (54.0%) were successfully cured or completed treatment; 7/98 (7.1%) were lost to follow-up and 10/98 (10.2%) died during treatment.

Treatment Outcome (n=98)	**Number of patients n (%)**
Cured/Completed	53 (54.0)
Lost to follow-up	7 (7.1)
Died	10 (10.2)
Missing outcome	20 (20.4)

Table 6: Outcomes

Chapter Five: Discussion

5.0 Introduction

This section discusses the findings of this study considering the current literature and the study objectives. The aim of this study was to describe the incidence of linezolid-associated side effects in MDR/RR-TB patients receiving routine care at an outpatient treatment centre located in a tertiary level hospital in Johannesburg. This study found that linezolid associated side effects occurred in 21% of the patients that were included in the analysis.

5.1 Demographics characteristics of the patients' records

In this study, the patients who were on DR-TB treatment with linezolid in their treatment were 98 (43.9%) out of the 223 that fit the inclusion criteria. These patients were patients who were receiving care at Helen Joseph Hospital's TBFP as outpatients and had documented linezolid treatment in their files or on FIS. The mean age in this study was 37 compared to the Nix trial done in South Africa which had a mean age of 35 (Conradie et al., 2020). The proportion of the HIV positive patients was 76.5% and 21.4% were HIV negative. This was slightly higher than what the Nix Trial had which was 51% HIV positive patients (Conradie et al., 2020). The baseline CD4 was 145 cells/mm3 but there were 44 missing CD4 values. The baseline CD4 of this study was significantly lower than the Nix-Trial which had a mean of 343 cells/mm3 and only 5 missing baseline values (Conradie et al., 2020). This study had 60.3% of males as compared to 52% in the Nix-Trial (Conradie et al., 2020).

5.2 Incidence of linezolid associated side-effects

Linezolid-associated side effects occurred in 21% of our cohort which is just under the pooled incidence of the systematic review done Zhang et al. (2015) which found the incidence of linezolid

associated side effects were 35%. In our cohort, the four main linezolid-associated adverse events included anaemia (4.1%), peripheral neuropathy (13.2%), GI-related side effects (11.2%) and visual disturbances (1%). Peripheral neuropathy is the most common adverse event observed in most studies evaluating linezolid toxicity (Zhang et al., 2015; Conradie et al., 2022) which is consistent with our findings. However, in some studies a much higher rate of linezolid associated peripheral neuropathy was found. In the Nix-trial done in South Africa, 81% of patients reported peripheral neuropathy (Conradie 2020). Wasserman et al. found in the study they conducted in South Africa that anaemia occurred in 39% of patients and anaemia was the most common adverse event they recorded (Wasserman et al., 2022). Zhang et al. found that optic neuritis occurred in 8% of their cohort (Zhang et al., 2015). The fact that patients enrolled in clinical trials are systematically questioned about side effects at each study visit may explain the higher incidence of linezolid toxicity identified than in our study that used routinely collected clinical data.

5.3 Severity of adverse events

In the whole cohort, there were no cases that were graded 4 (potentially life-threatening) or grade 5 (death). However, what needs to be noted is that a major limitation was that the majority of adverse events identified in during file review could not be graded due to insufficient information in the clinical record. In other studies, like the Nix-Trial 17% (n=19) of their cohort had serious adverse events of which 6 patients died during the trial (Conradie et al., 2020).

The highest grade recorded was grade 3 (severe) which is in less than 6% of the adverse event cases. Fifty-seven percent (57%) of the patients in the Nix-Trial had adverse events that were graded, grade 3 (severe) or higher. Most of the adverse events were mild (grade 1) and often did not require discontinuation or reduction of linezolid. In other research gradings lower than 3 were not discussed much. Our findings suggest that most patients tolerate linezolid treatment. And

others studies have found that linezolid containing treatment patients should be followed carefully especially in settings where the dosage is higher and longer than the current recommended treatment regimen.

5.4 Association of HIV status, gender and the incidence of linezolid associated side effects

The study found no statistically significant differences in the incidence of linezolid-associated side effects according to HIV status or sex. However, what should be noted is that the risk ratio for neuropathy in males is seven indicating an increased risk of neuropathy. This finding would need to be adjusted include other confounding factors and other probable causes. Conradie et al. (2020) and Zhang et al. (2015) also found that the rates of linezolid toxicity were similar between HIV positive and negative patients. However, this finding is limited by the small sample size.

5.5 Limitations

This research had a small sample; thus, the findings cannot be generalised. The numbers in the cohort were lower than expected and this could have been due to a number of reasons including the rapid decentralisation of DR TB treatment thus reducing the number of patients seen at the study site. The findings although are adverse events related to linezolid associated – note the possibility of the findings being influenced by other drugs. The study also had a lot of missing values which can be attributed to files missing information or the electronic files not being updated as the government now prioritises Electronic Drug Resistant Tuberculosis Register (EDRWeb) for reporting purposes. Thus incomplete notes were supplemented using TBFIS data and data still not found was recorded as missing data.

Chapter Six: Conclusion and recommendations

6.1 Conclusion

In this study, which was conducted in an outpatient treatment facility inside a tertiary level hospital in Johannesburg, on MDR/RR-TB patients getting routine, care the aim was to characterize frequency of adverse effects related with linezolid. In this study, 21% of the patients included in this analysis experienced adverse events related to linezolid.

Findings from this study demonstrates a lower incidence of linezolid-associated toxicity than has been previously described in the literature. This may be in part due to under-reporting or poor recording of side effects in the clinical record. However, in this study patients had no documentation of dose reduction or treatment interruptions of linezolid.,

The incidence of linezolid-associated side effects has been demonstrated outside of clinical trials and the rate at which the incidence occurs according to this research is low as opposed to the numbers that are seen in clinical trials. However, pooled systematic reviews have also demonstrated the low incidence in outpatient settings.

6.2 Recommendations

There should be better documentation of the adverse events in MDR/RR TB patients in order to ascertain the incidence of adverse events, severity and management of the adverse event. Recommendations would be to emphasize better documentation of adverse events in order for more research to be done in this area. Other recommendations would be for more research to be done on participants who experience adverse and the quality of life post adverse events and treatment. In addition, conducting this study on a larger cohort to ensure that the results are more

generalizable and more representative of the current effects of linezolid and if people experience toxicity.

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Appendix 1: Ethics Approval

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

29 November 2021

Mrs N Ngolele
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number:	BM21/10/21
Project Title:	The incidence of linezolid associated side effects in MDR/RR-TB patients receiving routine care at a tertiary hospital in Johannesburg, South Africa.
Approval Period:	19 November 2021 – 19 November 2024

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

Any further amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

For permission to conduct research using student and/or staff data or to distribute research surveys/questionnaires please apply via:
https://sites.google.com/uwc.ac.za/permissionresearch/home

The permission letter must then be submitted to BMREC for record keeping purposes.

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

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

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix 2: Hospital Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. R. Ncha
Chief Executive Officer
Tel :(011) 489-0306/1087
Fax :(011) 726-5425
E mail: Relebohile.Ncha@gauteng.gov.za
Date: 26 January 2022

Dear Nkateko Lebogang Ngolele

STUDY: The incident of linezolid associated side effects in MDR/RR-TB patients receiving routine care at a tertiary hospital in Johannesburg, South Africa.

RESEARCHERS: Nkateko Lebogang Ngolele

GP_202112_015

The above the study was discussed at the Research Committee meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research,
The researcher is expected to the following:

- Upon completion of the study, copy thereof should be submitted to Helen Joseph Hospital.
- It is the researcher's duty to collect the data from the relevant department after the Research Committee approved the study.

Please liaise with the HOD and Unit Manager or Sister in Charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the feedback of your study on completion of the research.
Thank you

Dr. M.D Mukansi
Helen Joseph Hospital
Research Chairperson

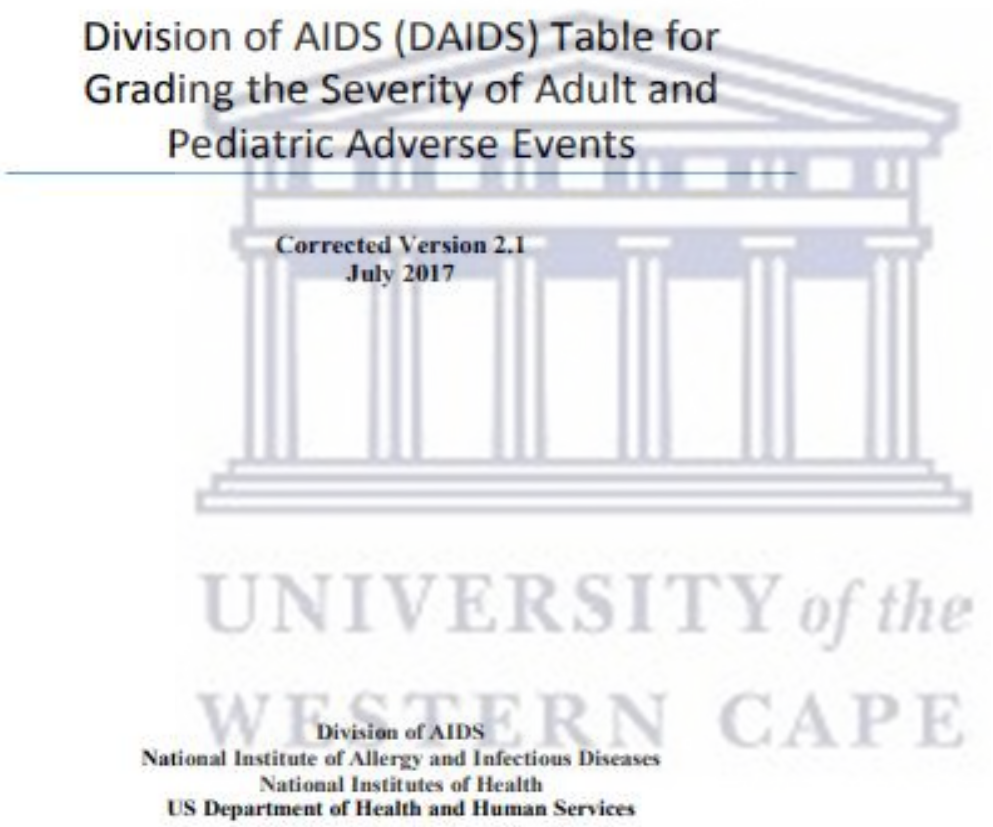
Approved

Dr. R. Ncha
Helen Joseph Hospital
CHIEF EXECUTIVE OFFICER
DATE: 27/01/27

Appendix 3: DAIDS Tables

https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

35 page document (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf



Appendix 4: Data Collection tool

Study ID	Age	Sex	Date of TB diagnosis	Resistance profile	Treatment outcome	HIV Status	ART Status	Linezolid therapy completed	Adverse event	Grading	Adverse events Mgt	Clinical notes regarding Adverse event