Optimizing the Safety of Multidrug-resistant Tuberculosis Therapy in Namibia

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Verbeteren van de veiligheid van de behandeling van multiresistente tuberculose in Namibië

(met een samenvatting in het Nederlands)

Proefschrift

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A Quote by Donna Flagg: When the Cure Is Worse Than the Disease

"Not only are the folks popping these pills not happy, but they now suffer from new problems that are caused by the drugs themselves".

http://www.huffingtonpost.com/donna-flagg/one-pill-away_b_777796.html
[Blog posted on 11/04/2010]

About the cover photo

This photo shows some dried up trees at Deadvlei in the Namib Desert, which is inhospitable to human life. Tuberculosis disease could be as old as the Namibia Desert, yet humankind hasn't been able to fully conquer it. If left untreated, TB deprives you of your full life potential and drains the vitality out of you, like the way the harshness of the Namib Desert drains life out of the trees depicted in the cover photo. However, looking above is the beautiful blue sky where rain and sunshine that sustain life, come from, symbolizing the hope and promise that TB treatment offers to patients.

Photo courtesy of https://pixabay.com/en/tree-desert-namibia-dead-vlei-64311/

TABLE OF CONTENTS

CHAPTER 1

General introduction

THE RE-EMERGENCE OF TUBERCULOSIS: A GLOBAL CONCERN

Reading current medical news and updates from journalists and the medical scientific community paints a gory and worrisome picture about the state of the tuberculosis (TB) epidemic across the world. [1] The news point towards a grim resurgence of the TB epidemic. [2–5] This epidemic is raging havoc primarily in low and middle income countries, while in high income countries; TB is rearing its ugly ahead again, wanting to attack once more in a more vicious form; a form that is resistant to the current anti-TB drugs. [1,6] In many low and middle income countries especially in sub-Saharan Africa, weak health systems have been contributory to this problem. [7] Are we, therefore, losing the opportunity of eliminating TB from the face of the earth? Why is it taking mankind so long to eradicate TB? These are some of the questions that are most likely to reverberate in one's mind while reviewing updates on the global TB epidemiology, from the year 2007 to date. A preeminent concern that is evident from these reports is the spectre of multidrug-resistant tuberculosis (MDR-TB).

> **Box 1: Quote by the Global TB Alliance [8]**
> "Today's TB treatments take too long to cure, are too complicated to administer, and can be toxic. Many people have negative interactions between commonly used antiretrovirals and TB treatment. People with TB must take drugs from 6 months to 2 years or longer—or risk developing more difficult to treat drug-resistant TB. Today, treatment for drug-resistant TB can take up to two years, and is so complex, expensive, and toxic that many patients are unable to access treatment. Further, the cost of curing MDR-TB can be staggering — literally thousands of times as expensive as that of regular treatment in some regions — posing a significant challenge to governments, health systems, and other payers. Of those who do, almost half will die."

Multidrug-resistant tuberculosis, therefore, can no longer be ignored, especially in developing countries, where the MDR-TB burden is highest. [9] Unlike drug-sensitive *Mycobacterium tuberculosis*, the treatment of MDR-TB takes a long time; is complex, and is frequently associated with the occurrence of a range of adverse drug reactions. [10–15] Some of these adverse drug reactions, such as ototoxicity, nephrotoxicity and hepatotoxicity, could severely diminish a person's health-related quality of life (HRQoL). [16–19] Besides, the global treatment success rates for MDR-TB have generally been poor, at around 48%, due to several factors, including patients' difficulties with adhering to their prescribed MDR-TB treatment regimens. [20,21] The occurrence of severe or serious treatment-related adverse events, along with other disease-related sequelae, may impair patients' ability to perform activities of daily life during or after MDR-TB treatment. [19,22] This calls for the routine monitoring, clinical assessment and management of adverse events among patients undergoing MDR-TB treatment, so

that their overall HRQoL can be preserved and the MDR-TB treatment success rates enhanced. [19] The treatment of MDR-TB and other forms of tuberculosis drug-resistance is even more complicated in patients who are also on concomitant antiretroviral (ARV) treatment for HIV [23] because of the overwhelming pill burden, medication adherence challenges, the possibility of drug-drug interactions; and the potential additive or overlapping adverse reactions of the anti-TB and ARV medicines. [24] In addition, children pose a unique challenge because of the lack of appropriate pharmaceutical dosage forms for this patient category [25,26] and the inability or difficulty of younger children to adequately describe the symptoms of the adverse events they may be experiencing. [27]

MDR-TB PATHOLOGY, EPIDEMIOLOGY AND TREATMENT

Tuberculosis is an ancient infectious disease caused by the *Mycobaterium tuberculosis* bacillus. [28] In a newly diagnosed patient who has never been treated before for TB, the bacterium is often susceptible to the current World Health Organization (WHO)-recommended first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin). [29] However, when the *M. tuberculosis* is resistant to both isoniazid and rifampicin, it is then termed as MDR-TB. [29] The leading cause of MDR-TB is the failure of patients to adhere to the first-line treatment of drug-susceptible TB. [30,31] Further, if a patient who is diagnosed with MDR-TB fails to correctly take his or her second-line medicines, the patient may develop extensively (XDR) or totally resistant strains of *Mycobacterium tuberculosis*. [4,32] XDR-TB involves resistance to isoniazid and rifampicin; resistance to any of the fluoroquinolones (such as levofloxacin or moxifloxacin) and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin). [33] Some experts have coined the term "programmatically incurable TB", to describe strains of *M. tuberculosis* that are resistant to almost all the older anti-TB drugs. [34]

Multidrug-resistant tuberculosis continues to disproportionately ravage populations living in low and middle income countries of the world. [35] In sub-Saharan Africa, MDR-TB is mainly prevalent in the countries with a high TB burden, such as Namibia, Botswana, Central African Republic, Chad, Congo, Ghana, Guinea-Bissau, Liberia, and Swaziland. [36] Namibia is a southern African country with a population of about 2.4 million people that is classified by the World Bank as an upper middle income country. [37] In Namibia, the rate of MDR-TB infection is high, but has been declining over the years. [38] The high HIV co-infection rate in the country poses a unique challenge for treating TB (drug susceptible or MDR-TB) concomitantly with HIV infection. [38] This is also true for the other countries in the southern African sub-region. [23,39]
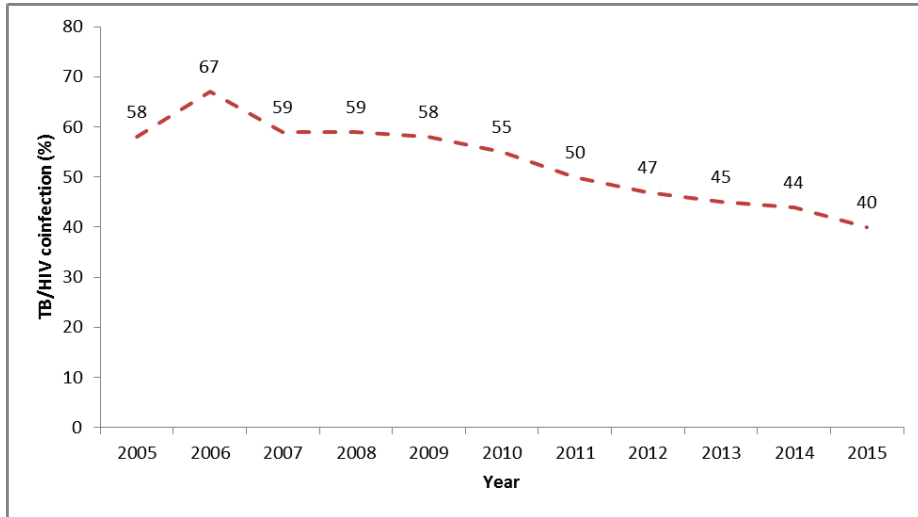
Figure 1: Trends in TB/HIV co-infection rates in Namibia: 2005-2014 [38,40]

For illustration, out of the 367 drug-resistant tuberculosis patients that were notified to the National Tuberculosis and Leprosy Treatment Program in Namibia in 2014, 360 (98%) knew their HIV status, while 169 (47%) of those who knew their HIV status were HIV positive. [41] Most of the 169 HIV positive MDR-TB patients (150 or 89%) were concomitantly on antiretroviral treatment (ART). The MDR-TB treatment success rate for the 2012 Namibian cohort was 68%; while the default rate of 9% and the death rate of 19% remained rather high, which showed that further work is needed to successfully treat MDR-TB in the country. [38] Most cases of MDR-TB in Namibia were associated with previous use of first-line anti-TB medicines, underscoring possible treatment adherence problems, and the inappropriate or incomplete use of anti-TB medicines by some patients. [42]

To-date (2017), the treatment regimen for drug-susceptible TB consists of an initial phase of two months of daily administration of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by a continuation phase of four months of daily rifampicin, isoniazid, and ethambutol, which makes the total duration of treatment to be six months. [43] The standard treatment for MDR-TB is also divided into two phases: the intensive and the continuation phase. [9] The intensive phase is a therapeutically critical phase that is designed to ensure that the majority of TB bacilli are killed and that drug-resistant bacilli have no chance to survive. This initial aggressive phase of therapy is then followed by a less intensive phase of treatment (the continuation phase) in which the patient is treated for a longer period with fewer anti-TB medicines because the population of live TB bacilli has now been drastically reduced, and the likelihood of having naturally resistant mutants is minimal. [44]

Typically, treatment regimens for MDR-TB are designed from drugs belonging to five therapeutic groups, in line with the WHO guidelines for the treatment of drug-resistant TB. [9,44,45] **Group 1** consists of the first-line oral drugs isoniazid; rifampicin; ethambutol; and pyrazinamide. In **Group 2** are the injectable drugs kanamycin; amikacin; capreomycin; streptomycin. **Group 3** is made up of the fluoroquinolones, notably levofloxacin and moxifloxacin; while **Group 4** consists of the oral bacteriostatic second-line drugs ethionamide; cycloserine; and paraaminosalicylic acid. The drugs in **Group 5** are those with unclear role in MDR-TB treatment; and include clofazimine; amoxicillin/clavulanate; high-dose isoniazid; clarithromycin.

The standardized intensive phase regimen for MDR-TB in Namibia is made up of at least five drugs, including an injectable agent and a fluoroquinolone, taken for at least six months and lasting for at least four months after culture conversion. [46] These drugs are kanamycin, ethionamide, levofloxacin, cycloserine, and pyrazinamide; plus ethambutol (subject to the *M. tuberculosis* drug sensitivity pattern); and a high dose of pyridoxine, to prevent peripheral neuropathy. The continuation phase comprises at least ethionamide, levofloxacin, and cycloserine; plus ethambutol (subject to the *M. tuberculosis* drug sensitivity pattern); and a high dose of pyridoxine, all concurrently taken for at least 18 months. [46]

According to the current Namibian TB treatment guidelines, doses of second-line anti-TB therapy must be directly observed for the entire duration of therapy, to ensure full adherence to treatment and to promote MDR-TB treatment success. [46] After completing the intensive phase of MDR-TB treatment, or after culture conversion; and when adequate arrangements for out-patient directly observed treatment, short-course (DOTS) strategy [47] have been made, the patients are then discharged for outpatient continuation treatment at a nearby health facility. The (DOTS)-plus strategy has been recommended by WHO as an effective strategy for promoting patients' adherence to second-line anti-TB drugs and improving MDR-TB treatment outcomes, albeit with variable success from around the world. [48–50]

ADVERSE EFFECTS AND SUCCESS RATES OF MDR-TB TREATMENT

Currently, the treatment of MDR-TB is complex and long, involving the daily administration of a combination of several medicines continuously for about two years. [9] This includes an initial eight-month period of daily injections, which some patients find excruciating. [51] Such a prolonged period of treatment may cause patients to become fatigued of taking their medicines, especially when they experience the unpleasant adverse reactions that tend to be notorious with second-line anti-tuberculosis medicines. [12,14,52,53] Although most adverse reactions are mild and self-limiting, patients may

occasionally encounter some severe or serious adverse reactions that may hinder them from completing their treatment as prescribed. [54] This makes it important for TB program managers and clinicians to actively monitor patients on MDR-TB treatment for the occurrence of adverse reactions, preferably through active pharmacovigilance, identifying patients who may be at risk of specific adverse reactions, and mitigating the risks. [55,56]

The success rate of MDR-TB treatment is still low for many countries, [29] including Namibia, causing a concern for the growing reservoir of MDR-TB and XDR-TB. [57–59] Yet, the successful treatment of MDR-TB requires that patients fully adhere to; and dutifully complete their prescribed second-line regimens. [9,47,60,61] This necessitates a delicate balancing act between the correct and complete treatment administration on the one hand; and the minimization of potential drug-related adverse reactions, on the other hand. In fact, patients and doctors have to make a difficult trade-off to accept the serious or severe non-fatal adverse effects that are associated with MDR-TB treatment so that patients may be cured of TB infection. [54] For example, a patient may consciously accept the risk of becoming deaf as a result of taking aminoglycosides so that the patient may get cured of TB. Does it mean that the cure is worse than MDR-TB disease? Not, necessarily so. This question is the essence of this thesis.

Such conscious trade-off by patients to accept or not to accept to endure the discomfort and unpleasantness of severe adverse effects of MDR-TB treatment in order for them to be cured may influence the way patients may rate their health-related quality of life; and whether to accept or reject MDR-TB treatment. Below is an excerpt from a case study that aptly illustrates the point.

> **Box 2: A case-study from the drug-resistant tuberculosis training network [62]**
> "Patient AB was a 54 year old male from Central Asia, who was on a failing first-line TB regimen. He was then started on a standard WHO eight month retreatment regimen (streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide for two months, followed by isoniazid, rifampicin, ethambutol, and pyrazinamide for one month; and then followed by isoniazid, rifampin, and ethambutol for five months). He began to complain of difficulty in hearing after taking one month of therapy. Otology evaluation at that point detected mild hearing loss via the whisper test. *Streptomycin was continued for one more month as part of the retreatment protocol because the benefit of the drug as a bactericidal agent was felt to outweigh the risk of significant ototoxicity.* The patient, however, refused further therapy because he was concerned that it would cause more hearing loss. Consequently, his health slowly worsened over the next six months while off anti-TB treatment."

Definitely, for patient AB described in the case study above, taking the anti-TB medicines was worse for him than the TB disease itself, clearly explaining why he refused to continue with his treatment, for concerns about suffering irreversible hearing loss

arising from treatment. Ototoxicity is a major adverse event of MDR-TB treatment that is associated with aminoglycoside and capreomycin use. [63]

SAFETY STUDIES IN SUB-SAHARAN AFRICA

To effectively monitor and manage the safety of current and new anti-TB medicines, functional pharmacovigilance systems are essential for national tuberculosis treatment programs. [64,65] Clinicians may be aware and, indeed, knowledgeable about the possible adverse effects of current anti-TB medicines, but the simultaneous use of multiple second-line anti-TB drugs for prolonged periods in a typical MDR-TB treatment regimen, sometimes with the concomitant use of medicines for treating other concurrent comorbidities, elevates the risk of potential serious adverse events in a patient. [55] The contribution of adverse drug reactions (ADRs) to poor therapeutic outcomes (death, treatment default and failure) in MDR-TB treatment in sub-Saharan Africa has not been well documented, except for some studies from South Africa. [15,66] This research gap needs to be addressed in future studies.

Pharmacovigilance systems employ a combination of passive and active surveillance strategies. [55,67] Passive or spontaneous reporting involves the spontaneous, and often, the voluntary reporting of suspected adverse events to a designated pharmacovigilance center, which reviews, determines causality, collates, analyses, provides feedback to reporters and transmits the reports to a national or global center for aggregation and further analysis. [67] Compared to other approaches, spontaneous reporting systems are easier to establish and to operate, [68] but they are often plagued by challenges in underreporting, poor data quality, temporal variation in reporting intensity, and lack of denominator data. [69,70] However, there are other active, more targeted and more intensive drug safety monitoring approaches that complement spontaneous reporting. [71] These methods are epidemiologically more robust, and include cohort event monitoring (CEM) and the use of longitudinal electronic medical records. [69,72]

In Africa, however, current research shows that the pharmacovigilance systems on the continent are largely new and are still developing. [73–75] Ampadu *et al.* have reported that about 65% (n=35) of the 55 African countries were full members of the WHO Programme for International Drug Monitoring (PIDM) as at the end of September 2015, with the first country joining the PIDM in 1992. [76] Notably, these 35 African countries contributed less than 1% of the global reports in the WHO database of spontaneous pharmacovigilance reports, VigiBase®. [76] In the VigiBase® analysis that was conducted by Ampadu *et al.*, almost one third of the reports from Africa pertained to HIV and AIDS treatment; while it was only 1.9% for the anti-tuberculosis the drugs. [76] This highlights a disconnection between the burden of disease profile in African

countries and the spontaneous reporting of suspected adverse events in VigiBase® by the continent. With the current increased funding levels for priority diseases like tuberculosis, HIV and malaria in Africa, [77] there is an opportunity to strengthen pharmacovigilance systems on the continent through public health programs. [78–80] Huff-Rousselle and colleagues have provided a detailed account of how Zambia has learnt from herself and other country experiences in strengthening her pharmaco-vigilance systems, which could benefit other countries in a similar situation. [81] Of particular note, the Strengthening Pharmaceutical Systems (SPS) program of the United States Agency for International Development (USAID) that was implemented by Management Sciences for Health (MSH), has recommended a holistic systems approach to strengthening pharmacovigilance systems in developing countries. [82] This approach combines the six WHO health systems building blocks [83] and the systemic capacity building framework described by Potter and Brough, [84] focusing on structures, systems, infrastructure, staff, skills, tools and other resources for supporting medicine safety activities. Namibia used this approach in establishing her national Therapeutics Information and Pharmacovigilance Center (TIPC) in 2008 that is responsible for conducting and coordinating pharmacovigilance activities. [85]

AIM AND OBJECTIVE OF THE THESIS

The aim of this thesis was to investigate real-world safety of second-line anti-TB medicines in the context of the national MDR-TB treatment program in Namibia. The objectives were (i) to determine the occurrence, risk factors and clinical management of adverse events associated with MDR-TB treatment; (ii) examine the epidemiology of serious adverse events of aminoglycosides in the presence or absence of HIV infection, with or without antiretroviral therapy (ART); and (iii) assess the link between the occurrence of adverse events and patients' perception of their health-related quality of life (HRQoL) at the end of MDR-TB treatment, in Namibia.

THESIS OUTLINE AND OVERVIEW

The thesis is organized into four main chapters. **Chapter 1** provides a general overview of the research topic, the aim and objectives of the research.

Chapter 2 explores the occurrence of adverse events during MDR-TB treatment, their associated factors, the role of HIV co-infection and the impact of adverse events on patients' HRQoL. In **Chapter 2.1**, the prevalence, profile and outcome of adverse events that are associated with the treatment of MDR-TB and the possible influence of HIV

disease on the occurrence of adverse events, are explored. **Chapter 2.2** compares the absolute risks and risk factors for the commonly observed adverse events during MDR-TB treatment in HIV-infected and HIV-uninfected patients. Subsequently, in **Chapter 2.3**, the incidence of the symptomatic moderate-to-severe adverse events during treatment of MDR-TB and their outcomes are determined and then compared by patients' HIV co-infection status. Finally, **Chapter 2.4** assesses the HRQoL of patients completing MDR-TB treatment in Namibia and evaluates whether the occurrence of adverse events influenced patients' rating of their HRQoL.

Chapter 3 focuses on the otological and renal safety of aminoglycosides or capreomycin. These injectable medicines are crucial for the intensive phase of MDR-TB treatment. The protracted use of aminoglycosides and capreomycin in MDR-TB treatment is known to cause dose-dependent irreversible hearing loss, requiring hearing aids, cochlear implants or rehabilitation. Therapeutic drug monitoring and regular audiological assessments may help to predict, prevent or detect the onset of hearing loss in patients on aminoglycoside or capreomycin treatment, but these services are not always available or affordable in many developing countries. Therefore, **Chapter 3.1** opens up this enquiry by evaluating the association between the use of streptomycin, amikacin, kanamycin and capreomycin in TB treatment and the global pharmacovigilance reporting of ototoxicity (deafness or hearing loss, tinnitus and vertigo); together with the associated factors. This is followed by **Chapter 3.2** that compares the cumulative incidence of hearing loss among patients treated for MDR-TB with amikacin or kanamycin-containing regimens, based on real-life clinical practice in Namibia. The same study also identifies the patients who are most-at-risk of hearing loss. **Chapter 3.3** wraps up this section by comparing renal insufficiency among MDR-TB patients treated with kanamycin-based regimens with those concomitantly treated with tenofovir disoproxil fumarate (TDF) or other ART regimens in Namibia.

Chapter 4 is the concluding chapter of the thesis. This chapter presents a general discussion of the benefits and limitations of the research on the real-world safety of medicines used for treating MDR-TB. Specifically, therapeutic challenges and gaps in MDR-TB treatment are reviewed; concerns about the weaknesses of pharmacovilance systems in most low and middle income countries are elaborated; and methodological challenges of comparing the benefits and the risks of the medicines using observational methods are discussed. The clinical and policy implications of all study findings are presented. Finally, areas for future research are identified, which could help us to understand better the safety and tolerability of current and new medicines used in MDR-TB treatment.

REFERENCES

1. Ditiu L. We Cannot Deny It Anymore. TB is the New Global Health Emergency. [Internet]. Stop TB Partnership. 2016 [cited 2017 Jan 25]. Available from: http://www.stoptb.org/news/stories/2016/ns16_045.asp

2. Livingstone G. We are losing the fight against TB, warns WHO [Internet]. The Independent. 2012 [cited 2017 Jan 25]. Available from: http://www.independent.co.uk/life-style/health-and-families/health-news/we-are-losing-the-fight-against-tb-warns-who-7742360.html

3. Hope J. Why we're losing the war on TB [Internet]. Daily Mail Online. [cited 2017 Jan 25]. Available from: http://www.dailymail.co.uk/health/article-88121/Why-losing-war-TB.html

4. Reichman LB. TIMEBOMB revisited 10 years later: can we sustain progress or are we losing the war? Int J Tuberc Lung Dis. 2013;17(11):1377–82.

5. Adams P. Losing the Fight Against Tuberculosis [Internet]. The New York Times. 2015 [cited 2017 Jan 25]. Available from: https://www.nytimes.com/2015/01/06/opinion/losing-the-fight-against-tuberculosis.html?_r=0

6. Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? Clin Microbiol Infect. Elsevier; 2013;19(10):889–901.

7. Bain LE, Clovis NC. Winning the battle and losing the war? Where public health is getting it wrong in the current fight against HIV-AIDS and tuberculosis in Sub-Saharan Africa. Pan Afr Med J. 2015;21:75.

8. TB Alliance. Inadequate Treatment [Internet]. [cited 2017 Jan 12]. Available from: https://www.tballiance.org/why-new-tb-drugs/inadequate-treatment

9. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland; 2008.

10. Sturdy A, Goodman A, José RJ, Loyse A, O'Donoghue M, Kon OM, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. J Antimicrob Chemother. 2011;66(8):1815–20.

11. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc lung Dis. 2004;8(11):1382–4.

12. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc lung Dis. 2007;11(12):1314–20.

13. Furin JJ, Mitnick CD, Shin SS, Bayona J, Becerra MC, Singler JM, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc lung Dis. 2001;5(7):648–55.

14. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. Int J Tuberc lung Dis. 2010;14(3):275–81.

15. van der Walt M, Lancaster J, Odendaal R, Davis JG, Shean K, Farley J. Serious treatment related adverse drug reactions amongst anti-retroviral naïve MDR-TB patients. PLoS One. 2013;8(4):e58817.

16. Patel P, Ramanuj V, Bala D. Assessment Quality of Life (QoL) of TB patients registered in Tuberculosis units of Ahmedabad Municipal Corporation area by using WHO Short Form -36. Sch J Appl Med Sci. 2014;2(6F):3303–6.

17. Muniyandi M, Rajeswari R, Balasubramanian R, Nirupa C, Gopi PG, Jaggarajamma K, et al. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. Int J Tuberc lung Dis. 2007;11(8):887–92.

18. Sharma R, Yadav R, Sharma M, Saini V, Koushal V. Quality of Life of Multi Drug Resistant Tuberculosis Patients : a Study of North India. Acta Med Iran. 2014;52(6):448–53.

19. Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. Int J Infect Dis. 2015;32:68–75.

20. World Health Organization (WHO). Global Tuberculosis Report, 2014. Geneva, Switzerland; 2014.

21. World Health Organization (WHO). MDR-TB 2014 Update. Geneva, Switzerland; 2014.

22. Ahmad N, Javaid A, Syed Sulaiman SA, Basit A, Afridi AK, Jaber AAS, et al. Effects of Multi-drug Resistant Tuberculosis Treatment on Patients' Health Related Quality of Life: Results from a Follow Up Study. Hasnain SE, editor. PLoS One. Public Library of Science; 2016 Jul 28;11(7):e0159560.

23. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, et al. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. PLoS One. 2011;6(7).

24. Laurenzi M, Ginsberg A, Spigelman M. Challenges Associated with Current and Future TB Treatment. Infect Disord - Drug Targets. 2007;7:105–19.

25. The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide. Second. Boston, USA; 2015.

26. Taneja R, Furin J, Maheshwari HK. Paediatric formulations of second-line anti-tuberculosis medications: challenges and considerations. Int J Tuberc Lung Dis. 2015;19(12):61–9.

27. World Health Organization. Promoting Safety of Medicines for Children. World Health. Geneva: WHO; 2007.

28. Smith I. Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. Clin Microbiol Rev. 2003;16(3):463–96.

29. World Health Organization. Multidrug-resistant tuberculosis (MDR-TB). Geneva; 2016.

30. Marahatta SB. Multi-drug resistant tuberculosis burden and risk factors: an update. Kathmandu Univ Med J (KUMJ). 2010;8(29):116–25.

31. World Health Organization. What is multidrug-resistant tuberculosis (MDR-TB) and how do we control it? WHO. World Health Organization; 2016.

32. Matteelli A, Roggi A, Carvalho AC. Extensively drug-resistant tuberculosis: epidemiology and management. Clin Epidemiol. 2014;6:111–8.

33. World Health Organization (WHO). Drug-resistant TB: XDR-TB FAQ. WHO website. World Health Organization; 2016.

34. Dheda K, Limberis JD, Pietersen E, Phelan J, Esmail A, Lesosky M, et al. Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: a prospective cohort study. Lancet Respir Med. 2017;2600(16):1–13.

35. World Health Organization (WHO). Global Tuberculosis Report, 2016. Geneva, Switzerland; 2016.

36. Countries with TB - High & low burden TB countries [Internet]. TBFACTS.ORG. [cited 2017 Jan 25]. Available from: http://www.tbfacts.org/countries-tb/

37. The World Bank. Namibia | Data [Internet]. 2016 [cited 2017 Jan 25]. Available from: http://data.worldbank.org/country/namibia

38. Ministry of Health and Social Services (MoHSS). National Tuberculosis and Leprosy Control Programme 2014/2015 Annual Report. Windhoek; 2015.

39. Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer PE, Satti H. Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. PLoS One. 2009;4(9):e7186.

40. Ministry of Health and Social Services (MoHSS). National Tuberculosis and Leprosy Programme Annual Report : 2015-2016. Windhoek; 2016.

41. Ministry of Health and Social Services (MoHSS). The Namibia Aids Response Progress Report 2015. Windhoek; 2015.

42. Ricks PM, Mavhunga F, Modi S, Indongo R, Zezai A, Lambert LA, et al. Characteristics of multidrug-resistant tuberculosis in Namibia. BMC Infect Dis. 2012;12(1):385.

43. World Health Organization (WHO). Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010.

44. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis-2011 update. 2011th ed. Geneva: WHO; 2011.

45. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis (2016 Update). Geneva: WHO; 2016.

46. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 3rd ed. Windhoek: MoHSS; 2012.

47. World Health Organization (WHO). What is DOTS? A Guide to Understanding the WHO-recommended TB Control Strategy Known as DOTS. Maher D, Mikulencak M, editors. Geneva: WHO; 1999.

48. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet. 2005;365(9456):318–26.

49. Arora VK, Sarin R, Singla R, Khalid UK, Mathuria K, Singla N, et al. DOTS-Plus for Patients with Multidrug-resistant Tuberculosis in India : Early Results After Three Years. Indian J Chest Dis Allied Sci. 2007;49(75–79).

50. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: A systematic review and meta-analysis of published studies. Infect Dis Poverty. 2017;6(1):1–8.

51. Medecins Sans Frontiers (MSF) | Doctors without borders. No more injections! [Internet]. Online Blog. 2011 [cited 2017 Feb 11]. Available from: http://blogs.msf.org/en/patients/blogs/tb-me/no-more-injections

52. Rathod KB, Borkar MS, Lamb AR, Suryavanshi SL, Surwade GA, Pandey VR. Adverse events among patients of multi drug resistant tuberculosis receiving second line anti TB treatment. Int J Sci Reports. 2015;1(6):253.

53. Tag El Din MA, El Maraghy AA, Abdel Hay AHR. Adverse reactions among patients being treated for multi-drug resistant tuberculosis at Abbassia Chest Hospital. Egypt J Chest Dis Tuberc. 2015;64(4):939–52.

54. Avong YK, Isaakidis P, Hinderaker SG, Van den Bergh R, Ali E, Obembe BO, et al. Doing No Harm? Adverse Events in a Nation-Wide Cohort of Patients with Multidrug-Resistant Tuberculosis in Nigeria. PLoS One. 2015;10(3):e0120161.

55. World Health Organization (WHO). A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: Enhancing the safety of the TB patient. Geneva: World Health Organization; 2012.

56. Systems for Improved Access to Pharmaceuticals and Services (SIAPS). Preventing and Minimizing Risks Associated with Antituberculosis Medicines to Improve Patient Safety. Arlington, Virginia: Management Sciences for Health (MSH); 2013.

57. Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. Br Med Bull. Oxford University Press; 2005;73–74(1):17–24.

58. Prasad R. Multidrug and extensively drug-resistant TB (M/XDR-TB): problems and solutions. Indian J Tuberc. 2010;57(4):180–91.

59. Günther G. Multidrug-resistant and extensively drug-resistant tuberculosis: a review of current concepts and future challenges. Clin Med (Northfield Il). 2014;14(3):279–85.

60. Mkopi A, Range N, Lwilla F, Egwaga S, Schulze A, Geubbels E, et al. Adherence to Tuberculosis Therapy among Patients Receiving Home-Based Directly Observed Treatment: Evidence from the United Republic of Tanzania. PLoS One. 2012;7(12):1–7.

61. Migliori GB, Dheda K, Centis R, Mwaba P, Bates M, O'Grady J, et al. Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa. Trop Med Int Heal. 2010;15(9):1052–66.

62. DR-TB Training Network. Clinical Case Discussion 018: High risk for hearing loss [Internet]. 2013 [cited 2017 Jan 9]. Available from: https://drtbnetwork.org/clinical-case-series/018-high-risk-hearing-loss

63. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5.

64. Jeetu G, Anusha G. Pharmacovigilance: a worldwide master key for drug safety monitoring. J young Pharm. 2010;2(3):315–20.

65. World Health Organization (WHO). Pharmacovigilance: ensuring the safe use of medicines. World Health. 2004;1–6.

66. Schnippel K, Berhanu RH, Black A, Firnhaber C, Maitisa N, Evans D, et al. Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. Int J Infect Dis. BioMed Central; 2016;16(1).

67. World Health Organization (WHO). The Safety of Medicines in Public health programmes: Pharmacovigilance an essential tool. Geneva: WHO; 2006.

68. Saha PS. Starting-Up A Pharmacovigilance Network from Scratch : A Brief Plan. J Pharm Res Clin Pract. 2014;4(1):58–66.

69. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: Complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75–81.

70. Goldman SA, Koch-Weser J, Sellers E, Zacest R, Green D, Reidenberg M, et al. Limitations and strengths of spontaneous reports data. Clin Ther. 1998;20:C40–4.

71. World Health Organization (WHO). Active tuberculosis drug-safety monitoring and management. Geneva; 2015.

72. Norén GN, Edwards IR. Modern methods of pharmacovigilance: detecting adverse effects of drugs. Clin Med (Northfield Il). Royal College of Physicians; 2009 Oct;9(5):486–9.

73. Isah AO, Pal SN, Olsson S, Dodoo A, Bencheikh RS. Specific features of medicines safety and pharmacovigilance in Africa. Ther Adv Drug Saf. 2012 Feb 1;3(1):25–34.

74. Strengthening Pharmaceutical Systems Program (SPS). Safety of medicines in sub-Saharan Africa: Assessment of pharmacovigilance systems and their performance. Arlington, Virginia; 2011.

75. Dodoo ANO, Ampadu HH. Pharmacovigilance in Africa. Mann's Pharmacovigilance. Oxford, UK: John Wiley & Sons, Ltd; 2014. p. 299–301.

76. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, et al. Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase®. Drug Saf. Springer; 2016 Apr;39(4):335–45.

77. Tan DH, Upshur RE, Ford N, McNeil W, Price-Smith A, Menzies D, et al. Global plagues and the Global Fund: Challenges in the fight against HIV, TB and malaria. BMC Int Health Hum Rights. 2003;3(1):2.

78. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance Activities in 55 Low- and Middle-Income Countries. Drug Saf. 2010;33(8):689–703.

79. Xueref S, Daviaud J, Pal S, S. X, J. D, S. P. The Global Fund and pharmacovigilance systems in resourcelimited settings. Lancet. 2013;381(9875):1360.

80. Miller V, Nwokike J, Stergachis A. Pharmacovigilance and global HIV/AIDS. Curr Opin HIV AIDS. 2012;7(4):299–304.

81. Huff-Rousselle M, Simooya O, Kabwe V, Hollander I, Handema R, Mwango A, et al. Pharmacovigilance and new essential drugs in Africa: Zambia draws lessons from its own experiences and beyond. Glob Public Health. 2007;2(2):184–203.

82. Strengthening Pharmaceutical Systems (SPS) Program, USAID. Supporting Pharmacovigilance in Developing Countries: The Systems Perspective. Arlington, Virginia: Management Sciences for Health (MSH); 2009.

83. World Health Organization (WHO). Everybody's business: strengthening health systems to improve health outcomes: WHO's framework for action. Geneva: WHO; 2007. 1-56 p.

84. Potter C, Brough R. Systemic capacity building: A hierarchy of needs. Health Policy Plan. 2004;19(5):336–45.

85. Sasman C. Namibia Launches Medicine Database. New Era Newspaper Namibia. Windhoek, Namibia; 2008 May 13;[Cited 2017 Feb 13] https://www.newera.com.na.

CHAPTER 2

An overview of adverse events during drug-resistant tuberculosis treatment

Chapter 2.1

The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia

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ABSTRACT

Objective: Namibia faces a dual burden of HIV/AIDS and tuberculosis (TB). In 2010, HIV prevalence was 18.8%, the TB case notification rate was 634 cases per 100,000 population and the TB/HIV co-infection rate was 58%. There were 372 cases of drug-resistant TB (DR-TB) in 2009. The objective of this study was to assess the prevalence, profile and outcome of adverse events (AEs) associated with treatment of DR-TB and to explore possible influences of HIV disease on the occurrence of adverse events.

Methods: This was a cross-sectional descriptive study. After ethical approval, data were collected from treatment records of all patients treated for DR-TB at the study facility between January 2008 and February 2010 using a structured data collection form.

Results: A total of 141 adverse events of varying severity were experienced in 90% (53/59) of patients.The TB/HIV co-infection rate was 53% (n=31). The prevalence of gastrointestinal tract adverse events (abdominal pains, constipation, diarrhea, nausea and vomiting) was 64%, tinnitus 45%, joint pain 28%and decreased hearing 25%. Abdominal pains, rash, nausea, decreased hearing and joint pain were more common in HIV infected than in HIV uninfected patients.

Conclusions: Adverse events of varying severity are common during treatment of DR-TB, particularly in the intensive phase of therapy. Some adverse events were more prevalent in DR-TB patients co-infected with HIV. The study concludes that the characteristics and risk factors of serious adverse events should be further examined.

INTRODUCTION

Tuberculosis (TB) exerts a huge burden of disease in Namibia, with a case notification rate (CNR) of 634 cases per 100,000 population in 2009. [1] This is one of the highest tuberculosis CNRs in Africa. The TB/HIV co-infection rate was 58% in 2009. [1,2] Resistance to first-line regimens is a growing issue and could be due to various factors, including sub-optimal patient adherence to treatment schedules and defaulting in treatment. [3] Namibia reported 372 cases of drug resistant TB (DR-TB) in 2009, of which 74% of cases were`multi-drug resistant TB (MDR-TB), 22% poly-drug resistant TB and 5% were extensively drug resistant TB (XDR-TB). [1]

Although a number of studies [4–15] have examined the occurrence and characteristics of adverse events among patients on second-line anti-TB medicines, very few have specifically examined occurrence of adverse events in sub-Saharan Africa, [16] especially in the context of high HIV prevalence and high TB/HIV co-infection rates. Most reviewed studies have mainly focused on adverse events of either one or two anti-TB medicines, but not on the entire treatment regimen. [4–16]

This study describes the epidemiology of adverse events associated with treatment of DR-TB in a sub-Saharan country with a dual burden of TB and HIV. It further explores possible influences of HIV disease and antiretroviral treatment on the occurrence of adverse events.

The study thereby contributes to the existing body of epidemiologic and public health knowledge about treatment of DR-TB, focusing on a sub-Saharan country. This will assist managers of tuberculosis control programs, clinicians, and patients in similar socio-economic and epidemiologic settings in making evidence-based decisions for optimizing treatment outcomes for DR-TB patients, particularly in HIV co-infected patients. In this context, we aimed at assessing the profile, frequency and outcomes of adverse events associated with the use of second-line anti-TB medicines. The specific objectives of the study were:

1. To determine the types and frequency of adverse events associated with the use of second-line anti-TB medicines in a selected DR-TB treatment facility in Namibia.
2. To describe the characteristics, duration and outcomes of the adverse events, focusing on differences in adverse event occurrence between HIV infected and HIV uninfected persons.

METHODS

Settings

The study was conducted in a 25-bed district hospital DR-TB ward with the second larg-est number of patients on DR-TB treatment in Namibia. Patients diagnosed with DR-TB are hospitalized in this TB ward, which is physically isolated from the rest of the wards in the hospital. This isolation is part of the infection control measures put in place at the facility to minimize nosocomial transmission of Mycobacteria tuberculosis. The pa-tients with DR-TB infection are initiated on second-line treatment for about six months of intensive chemotherapy that includes injectable agents (amikacin, kanamycin or ca-preomycin). Until 2008, amikacin was the preferred aminoglycoside but this was later changed to kanamycin from 2009 onwards. The daily patient doses for each medicine used in the regimen were calculated and individualized according to the recommended World Health Organisation (WHO) body weight-based dosing scheme for anti-TB drugs (Table 3). Continuation therapy using oral anti-TB agents that includes a fluoroquino-lone is maintained through an outpatient directly observed treatment short-course (DOTS)-plus programme. This DOTS-plus treatment is implemented through the health center closest to the patient. Patients on continuation therapy visit the health facility every day (Monday - Friday) for daily doses of second-line anti-tuberculosis medicines. Doctors and nurses elicit information on adverse events from patients and record them on a structured, pre-printed DR-TB treatment side effects monitoring form.

Study participants and data collection

For this cross-sectional descriptive study, the study population included all patients treated with second-line anti-TB medicines at the DR-TB treatment facility from 01 January 2008 to 24 February 2010. Treatment records were reviewed for all the patients treated for DR-TB during this period. Further, data on patient demographics, Mycobacterium tuberculosis drug resistance, medications and other clinical variables, including occurrence of adverse events and the characteristics of the adverse events, were collected from patient records using a structured data collection form. Since the present study did not involve direct contact with patients, informed patient consent was not required. Ethical approval of the study protocol was obtained from the research unit of the Ministry of Health and Social Services of Namibia (MoHSS) and the Higher Degrees Committee of the University of the Western Cape, South Africa.

Occurrence of adverse events and the analysis of data

The main outcome variable was the occurrence of adverse events. Further, a detailed characterization of the adverse events was conducted, which included: the adverse event description, time to onset of the adverse event, grading of severity of the adverse

event, duration of the adverse event, actions taken to clinically manage the adverse event, and the outcome of the adverse event. Data were single-entered into Epi Info version 3.5.3 and the accuracy of entry verified against the original paper forms. The data were further checked for any errors and then analyzed using descriptive statistics. Absolute and relative frequency counts and measures of central tendency (mean, median and mode) were calculated. Measures of dispersion including range, interquartile range and standard deviation were also calculated. Student's T-tests were used to assess differences in age and weight between the genders. A P-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Epi Info version 3.5.3., while Microsoft Excel® (2010) was used to draw charts.

RESULTS

Fifty-nine (59) patients were treated for DR-TB during the study period. There were more male patients than females (66% vs. 34%). The mean patient age was 34.7 ± 9.4 (SD) years (Table 1). Males were slightly older than females (36.9 versus 31 years;P=0.02). The mean baseline weight was 52.5 ± 11.3 (SD) kilograms (kg), with no statistically significant gender difference (53.6 ± 7.8 kg males, versus 49.8 ± 16.4 kg females; *P*=0.23). About one-third of patients were unemployed.

Almost all (92%) of the 59 patients had a prior history of treatment with either first-line or second-line anti-tuberculosis medicines. Approximately half of the patients (31/ 59 or 53%) were co-infected with the human immuno deficiency virus (HIV). Of the 31 HIV co-infected TB patients, 13 (42%) were on highly active antiretroviral treatment (HAART).

In total, there were fifteen different anti-tuberculosis medicines that were used by the patients included in this study (Table 3). Most of the patients were treated with DR-TB regimens containing pyrazinamide (93%) and ethionamide (92%). All patients were treated with an injectable anti-tuberculous agent (amikacin, kanamycin or capreomycin) during the intensive phase of treatment,with kanamycin being the most frequently used aminoglycoside in 54% of the patients. Fluoroquinolones (ciprofloxacin and levofloxacin) were used in almost all of the patients (98%), of which levofloxacin was used twice as much as ciprofloxacin (66% versus 32%).

There were 30 individualized regimens that were used in the intensive phase of treatment and 18 in the continuation phase of treatment. These individualized regimens were determined according to the drug sensitivity patterns of the infecting Mycobacterium tuberculosis strain.

Fifty-three of the 59 patients experienced at least one adverse event of varying severity grading (90% prevalence). 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 proportion of patients experiencing a given number of adverse events dramatically reduced from the intensive to the continuation phase of treatment (Figure 1).

Table 1: Demographic and clinical characteristics of the 59 patients treated with DR-TB therapy

Characteristic	n (%)
Gender	
Male	38 (64%)
Female	20 (34%)
Missing	1 (2%)
Age (years), SD	34.7 ± 9.4
Male	36.9 ± 8.4
Female	31.0 ± 10.2
Weight (kg), SD	52.5 ± 11.3
Male	53.6 ± 7.8
Female	49.8 ± 16.4
Occupation	
Unemployed	18 (31%)
Employed	20 (34%)
Student	1 (2%)
Missing	20 (34%)
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%)
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)

Table 1: Demographic and clinical characteristics of the 59 patients treated with DR-TB therapy (continued)

Characteristic	n (%)
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 of number of patients with HIV co-infection
SD=standard deviation; kg=kilogrammes; TB=tuberculosis; PTB=pulmonary tuberculosis; + = positive;
- = negative; EPTB=extra pulmonary tuberculosis; MDR=multidrug-resistant; XDR=extensively
drug-resistant; 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
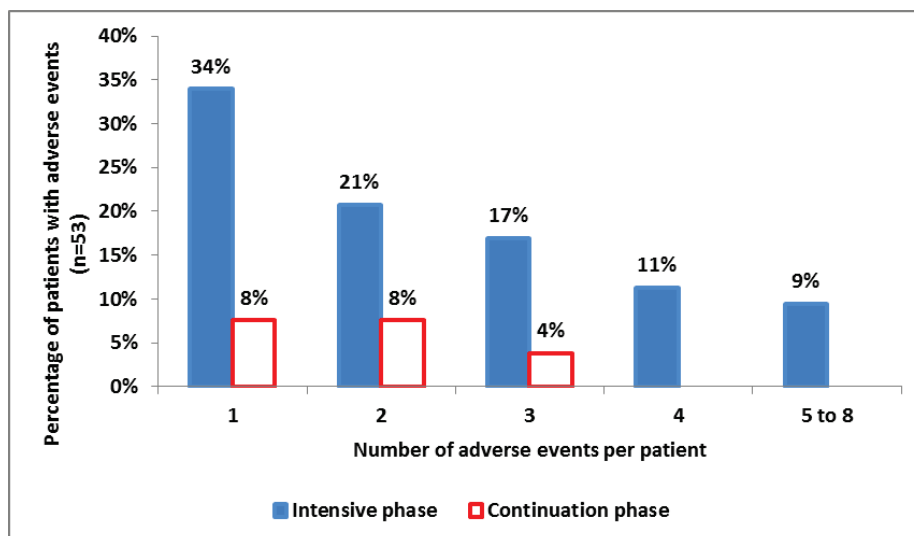
Figure 1: Distribution of percentage of patients by number of adverse events experienced per patient in the intensive and continuation phases of treatment

The average number of adverse events experienced by patients treated using specific anti-tuberculosis medicines ranged from one to three (Figure 2). Patients using regimens that contained streptomycin, capreomycin, cycloserine, and para-amino salicylic acid (PAS) experienced the highest average number (3) of adverse events, while patients using amoxicillin/ clavulanic acid and clofazimine experienced the fewest, with an average of one adverse event per drug. The rest of the medicines were associated with a similar average number of two adverse events per patient (Figure 2).

PAS= para amino salicylic acid
Number next to a drug name indicates the mean adverse events per patient treated with that drug
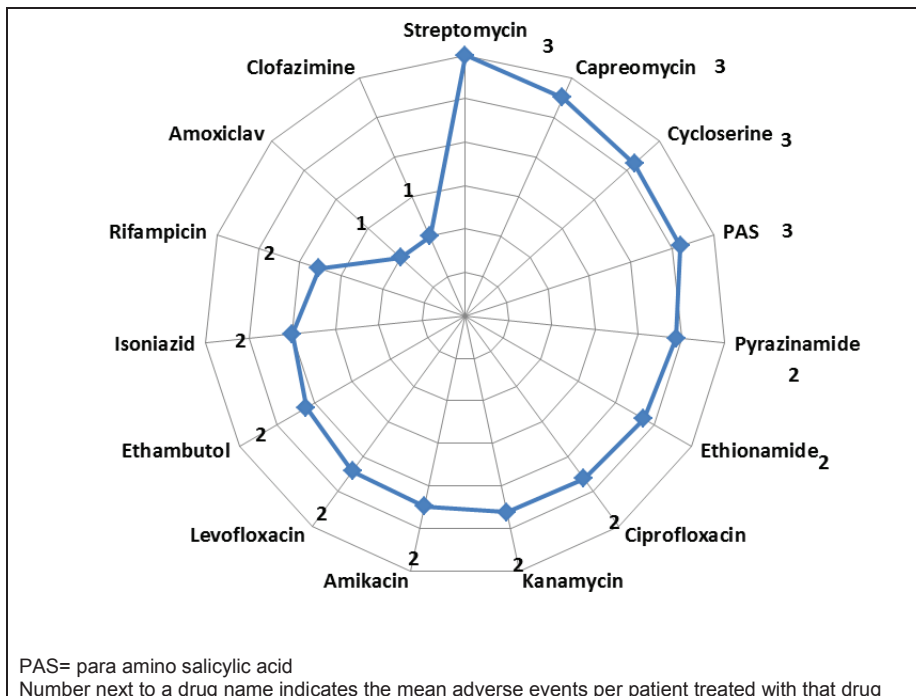
Figure 2: Average number of adverse events experienced per patient exposed to specific anti-tuberculosis drug

Hearing loss (decreased hearing), tinnitus, gastrointestinal tract (GIT)-related events (nausea, abdominal pains, vomiting, diarrhea and constipation) and joint pain were the predominant adverse events (Table 2). Five adverse events were more prevalent in HIV infected patients than in HIV uninfected patients (the figures in brackets show the excess frequency of occurrence in HIV infected patients as compared to HIV negative patients). These adverse events were: abdominal pains (22%); rash (16%); nausea (10%); decreased hearing (7%) and joint pain (6%). Contrarily, fever and fatigue are examples of adverse events that were reported less frequently by these patients (Figure 3).
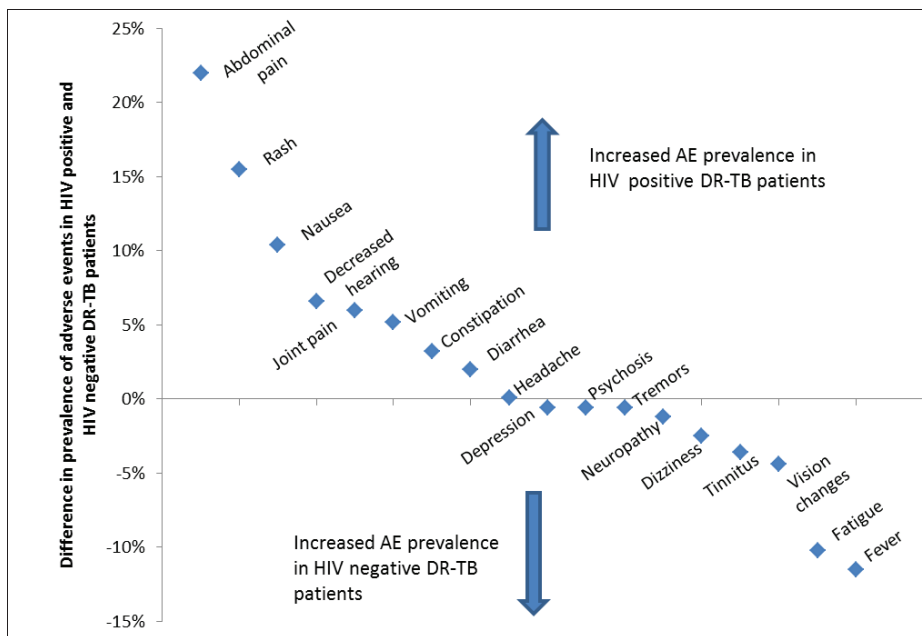
AE= adverse event; HIV= human immunodeficiency virus; DR-TB= drug-resistant tuberculosis

Figure 3: Comparison of difference in prevalence of adverse events in HIV positive and HIV negative DR-TB patients

Fourteen (93%) of the 15 reported cases of joint pain were observed in patients treated with pyrazinamide-containing regimens.

Seventy three percent of the moderate-to-severe adverse events lasted for more than three (3) months, while 60% of the mild adverse events resolved 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 four (4) out of 26 (15%) patients. Four (4) out of the 42 (9%) patients for whom data was available recovered from their adverse reactions with sequelae.

Table 2: Frequency of adverse events in both treatment phases; intensive and continuation phases respectively

Grouped adverse events	Specific adverse events	Both phases (N=53)*	%	Intensive phase (N=53)	%	Continuation phase (N=49) †	%
Hearing loss & Tinnitus	Tinnitus	24	45%	21	40%	3	6%
	Decreased hearing	13	25%	12	23%	1	2%
	Hearing loss & Tinnitus 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%
	GIT 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 to have experienced at least one DR-TB treatment-related adverse event. All 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 on continuation phase treatment or had completed treatment at the time of data collection. %= percent. Sum of column percentages may exceed 100% because a patient may experience more than one adverse event. GIT = gastrointestinal tract

Table 3: Prevalence of use and the weight-based dosing of specific anti-tuberculosis drugs in the treatment of drug-resistant tuberculosis in Namibia

Drug name	DRUG EXPOSURE		DOSING BY WEIGHT CLASS			
	Number of patients	Percent (n=59)	<33 KG	33–50 KG	51–70 KG	>70 KG (Maximum dose)
Pyrazinamide	55	93%	30–40 mg/kg daily	1000–1750 mg daily	1750– 2000 mg daily	2000– 2500 mg daily
Ethionamide	54	92%	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Levofloxacin	39	66%	Usual adult dose is 750 mg	750 mg	750 mg	750–1000 mg
Ethambutol	36	61%	25 mg/kg daily	800–1200 mg, daily	1200– 1600 mg daily	1600– 2000 mg daily
Kanamycin	32	54%	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Cycloserine	29	49%	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Amikacin	21	36%	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Ciprofloxacin	19	32%	20–30 mg/ kg daily	1500 mg 1500 mg	1500 mg	
Rifampicin	13	22%	10–20 mg/kg, daily	450–600 mg, daily	600 mg, daily	600 mg, daily
Para-aminosalicylic acid	5	8%	150 mg/kg daily			
Capreomycin	4	7%	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Isoniazid	4	7%	4–mg/kg daily or 8–12 mg, 3 x wk	200–300 mg daily or 450–600 mg, 3 x wk	300 mg daily or 600 mg, 3 x wk	300 mg daily or 600 mg, 3 x wk
Streptomycin	3	5%	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Clofazimine	1	2%	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			
Amoxicillin/ Clavulanate	1	2%	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			

Source: *WHO, (2006). Guidelines for the programmatic management of drug-resistant tuberculosis: 147-8.* mg=milligrammes; Kg=kilogrammes; wk = week

DISCUSSION

Adverse events of varying severity, particularly tinnitus, hearing loss, GIT-related adverse events and joint pains were experienced by most (90%) of the patients in-cluded in this study. Most of the adverse events were reportedly experienced in the intensive phase of DR-TB treatment. Some differences in the occurrence of adverse events were observed between patients who were HIV infected and those who were HIV uninfected. Abdominal pains, rash, nausea, decreased hearing and joint pain were among the adverse events more frequently reported by HIV infected patients, whereas fever and fatigue were reported relatively less frequently, when compared with HIV uninfected patients.

Chapter 2.1

The 90% prevalence of adverse events observed in the current study is higher than that reported in other studies, where it ranged from 69%-86%. [4–14,16] It was slightly lower than the 96% reported by Tupasi and colleagues in their study of 117 patients in the Philippines. [15] The reasons for the heterogeneity in the prevalence of adverse events across the various studies is unclear, but might be related to several possible factors such as: differences in definitions of adverse events terminologies across settings, whether the adverse event was symptomatic and patient-reported (subjective) or clinician-validated (objective), whether all or only the severe and serious adverse events were studied, variations in the use of specific anti-TB agents, and/or the differences in co-morbidities and other covariates between study settings. Our study's cohort is similar to other cohorts in terms of demographics and number of anti-TB medicines used and treatment duration. In addition, treatment was according to existing guidelines. [3,17] However, the HIV co-infection rate and the specific anti-TB agents used may differ between settings and this should be borne in mind when interpreting and comparing results of adverse events reported from different countries. Although the present study found the TB/HIV co-infection rate to be higher than that reported in Europe and South East Asia (where HIV prevalence rates are low), [6,13,18] it is lower than that observed for Lesotho, a country in Southern Africa, which has a high prevalence of HIV infection. [16]

The frequency of tinnitus (45%) in the present study was higher than the 5.1% - 24% range reported in the literature, [4,14,15] while that of hearing loss (25%) was within the range of 6.7% - 33% reported in the literature. [5,11,14,15] From the review of the literature, the reported rates of ototoxicity (tinnitus and hearing loss) ranged from 12% to 42%. [6,7,16] Our study found an almost double rate of ototoxicity, when compared to the 36% reported by Seung *et al.*,[16] whose study population and HIV prevalence rates are similar to our population. It is unclear why this is so, but one possible reason could be that the majority of patients in the Seung study were still in the early stages of treatment, hence not all potential adverse events may have occurred by the time of completion of their study. The high degree of heterogeneity of ototoxicity observed in the literature could have been brought about by differences in the use of specific ototoxic anti-TB agents, as well as by the differences in the profiles of co-morbidities in the different patient population groups of the various studies.

Ototoxicity (tinnitus and decreased hearing) is predominantly associated with the use of parenteral anti-tuberculous agents (aminoglycosides and aminopeptides). [19–24] The drug-specific rate of patient-reported tinnitus in the current study ranged from 33%- 50%, while hearing loss was 13% - 67%. These findings are above the range of 15.4% - 33% reported in studies conducted elsewhere. [5,19,20] The high prevalence of tinnitus and hearing loss found in our study is probably because they were symptomatic or patient-reported (subjective) and may not have been clinically

validated by audiometric tests. In addition, there could have been 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. Additionally, there are possibilities of interactive effects from HIV disease and the concomitant use of antiretroviral medicines, which may have contributed to this high rate of ototoxicity. This needs further investigation to uncover the possibility of these interactive effects.

The gastrointestinal tract (GIT)-related adverse events were the second most observed group of adverse events, reported by 64% of the patients. The specific GIT-related adverse events were: nausea (23%), abdominal pain (17%), vomiting (11%), diarrhea (9%), and constipation (4%). The frequency of occurrence of these specific GIT-related adverse events fall within the wide range (10.8% - 100%) which has been reported in the literature. [4,6,7,11,14–16] Since some studies have reported higher rates of specific GIT-related adverse events, it is possible that patients in our study may have selectively under-reported these adverse events during the course of their treatment.

The possibility of drug-drug interactions, [10] drug-disease and disease-disease interactions should be reflected on in the present study, particularly considering that an average of five different anti-TB agents were used by each patient in the study and that over 50% of the patients had HIV co-infection, 42% of whom were on concomitant antiretroviral medication.

In our study, adverse events were severe and warranted discontinuation of the suspected offending medicine in 15% of patients. This prevalence of treatment discontinuation is lower than that reported in the literature. [4,5,12,14] Generally, our findings are similar to the findings of Furin *et al.* (2001) that adverse events of the anti-TB medicines were bearable and did not cause discontinuation of the treatment apart from the occasional suspension of an offending agent in 11.7% of the patients. [11]

Strength of the study

The data used in this study reflect real-life DR-TB treatment practices and patient experiences. The cross-sectional descriptive design enabled us to examine and describe the prevalence and profile of adverse events in the patient sample. We were able to generate a tentative hypothesis that some adverse events occur more in DR-TB patients co-infected with HIV, which is clinically important when treating this sub-group of patients.

Limitation of the study

By using retrospective data, we encountered instances of missing patient treatment records and missing data on specific variables. Furthermore, it was not possible to perform qualitative causality assessment of the adverse events using the available data, especially given the paucity of laboratory data. The adverse events recorded on

the patients' side-effects monitoring form were based on patient-reported symptoms. Hence, there was a possibility of subjectivity and of selective under-reporting of adverse events by patients or the selective recording of adverse events by clinicians, which may have biased the results away from the true prevalence. Some symptoms of reported adverse events may have overlapped with symptoms of HIV/ AIDS. The small sample size and the use of data from one facility may not allow for generalization of findings beyond the studied sample.

CONCLUSIONS

This study found that adverse events, of varying severity, most commonly occur in the intensive phase of DR-TB treatment.While most patients tolerated the second-line anti-TB medicines used in Namibia's DR-TB treatment program, about 10% of patients experienced serious adverse events, with a possibility of suffering permanent disability. Some adverse events were more prevalent in DR-TB patients co-infected with HIV. The characteristics, magnitude of risk and risk factors of these serious and potentially permanent adverse events should be thoroughly examined and elucidated in subsequent prospective active surveillance pharmacovigilance or cohort studies. Therefore, clinicians, including pharmacists, should closely monitor and aggressively manage adverse events during the intensive phase of DR-TB treatment and should always consider the possibility of increased occurrence of adverse events in patients co-infected with HIV.

ACKNOWLEDGMENT

Chapter 2.1

REFERENCES

1. Ministry of Health and Social Services (MoHSS). National Tuberculosis and Leprosy Programme: Second Medium Term Strategic Plan for Tuberculosis and Leprosy, 2010-2015. Windhoek: MoHSS; 2010.

2. Ministry of Health and Social Services (MoHSS). Report on the 2008 National HIV Sentinel Survey. Windhoek: MoHSS; 2008.

3. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 2nd ed. Windhoek: MoHSS; 2006.

4. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc lung Dis. 2004 Nov;8(11):1382–4.

5. Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The Treatment of Multidrug-Resistant Tuberculosis in Turkey. N Engl J Med. Massachusetts Medical Society ; 2001 Jul 19;345(3):170–4.

6. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet. 2005;365(9456):318–26.

7. Törün T, Güngör G, Ozmen I, Bölükbaşi Y, Maden E, Biçakçi B, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc lung Dis. 2005 Dec;9(12):1373–7.

8. Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rüsch-Gerdes S, et al. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLoS One. 2007 Jan;2(11):e1126.

9. Nahar BL, Hossain AM, Islam MM, Saha DR. A comparative study on the adverse effects of two anti-tuberculosis drugs regimen in initial two-month treatment period. Bangladesh J Pharmacol. 2008 Jan 7;1(2):51–7.

10. Papastavros T, Dolovich LR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ. 2002 Jul 23;167(2):131–6.

11. Furin JJ, Mitnick CD, Shin SS, Bayona J, Becerra MC, Singler JM, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc lung Dis. 2001 Jul;5(7):648–55.

12. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc lung Dis. 2007 Dec;11(12):1314–20.

13. Lanternier F, Dalban C, Perez L, Bricaire F, Costagliola D, Caumes E. Tolerability of anti-tuberculosis treatment and HIV serostatus. Int J Tuberc lung Dis. 2007 Nov;11(11):1203–9.

14. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. Int J Tuberc lung Dis. 2010 Mar;14(3):275–81.

15. Tupasi TE, Gupta R, Quelapio MID, Orillaza RB, Mira NR, Mangubat N V, et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006 Sep;3(9):e352.

16. Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer PE, Satti H. Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. PLoS One. 2009 Jan;4(9):e7186.

17. World Health Organization (WHO). Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010.

18. Cain KP, Kanara N, Laserson KF, Vannarith C, Sameourn K, Samnang K, et al. The epide-miology of HIV-associated tuberculosis in rural Cambodia. Int J Tuberc lung Dis. 2007 Sep;11(9):1008–13.

19. Jager P De, Altena R Van. Hearing loss and nephrotoxicity in long-term aminoglycoside. Int J Tuberc Lung Dis. 2002;6(April):622–7.

20. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5.

21. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. Antimicrob Agents Chemother. 1989 Jun;33(6):797–800.

22. Nadol J. Hearing loss. N Engl J Med. 1993;329(15):1092–102.

23. Tan KH-V, Mulheran M, Knox AJ, Smyth AR. Aminoglycoside Prescribing and Surveillance in Cystic Fibrosis. Am J Respir Crit Care Med. American Thoracic Society; 2003 Mar 15;167(6):819–23.

24. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007 Jan;13(1):119–26.

Chapter 2.2

Adverse events during treatment of drug-resistant tuberculosis: a comparison between patients with or without human immunodeficiency virus co-infection

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ABSTRACT

Introduction: In settings such as Namibia with a high prevalence of human immunodeficiency virus (HIV) and drug-resistant TB (DR-TB) co-infection, interactions and adverse events associated with second-line anti-tuberculosis (TB) and antiretroviral medicines pose a unique challenge in the treatment of both infections.

Objective: Our main objective was to compare the absolute risks and risk-factors for commonly observed adverse events (occurring in > 20% of patients) during DR-TB treatment in HIV infected and HIV uninfected patients.

Methods: Retrospective cohort analysis of patients treated for DR-TB between January 2008 and February 2010 at the Kondja DR-TB ward in Namibia. Data were anonymously collected from patients' treatment records using a structured form. Data were then analyzed using descriptive statistics, while 2 x 2 contingency tables stratified by HIV status were employed to examine specific risk-factor and adverse event relationship, using Epi Info 3.4.3 statistical software.
Eighteen adverse events were studied but due to the small sample size of patients, only the four most frequent ones (occurring in > 20% of patients) were included in the risk-factor analysis. The risk-factors were; treatment period < 4 weeks, treatment with any HAART regimen, specific treatment with AZT-based HAART, cycloserine –based DR-TB regimen, amikacin –based DR-TB regimen, female gender, baseline body weight≤45kg and age 30≥years.

Results: Of the 57 drug-resistant tuberculosis patients included in the analysis, 31 (53%) were co-infected with HIV. DR-TB patients had comparable demographic and clinical characteristics; and similar exposure to specific DR-TB medicines by HIV status, except for age. HIV infected patients were on average 6.5 years older than HIV uninfected patients (p=0.007). Of the 18 studied adverse events, tinnitus (40%), joint pain (26%), hearing loss (23%) and nausea (21%) were the four most commonly observed events. Only abdominal pain had a statistically significant difference in the risk of occurrence in HIV infected patients compared with HIV uninfected patients (26% vs 4%, p = 0.02).
The risk ratios for the association between treatment with a cycloserine-based DR-TB regimen and the occurrence of joint pain were not much different between HIV infected and HIV uninfected patient groups (RR, HIV infected = 4.3, p=0.03; RR, HIV uninfected = 5, p=0.08). Similarly, although some differences in the risk ratios were observed between the two HIV status groups, the differences were not statistically significant for tinnitus, hearing loss and nausea. In some instances, HIV status appeared

to modify the effect of the association of some of the risk factors and adverse event occurrence, but the wide and overlapping confidence intervals are inconclusive.

Conclusion: Generally, the absolute risks and risk factors for adverse events were similar between HIV infected and HIV uninfected patients treated for drug-resistant tuberculosis in our Namibian cohort of 57 patients. Although our findings of comparable adverse event risks between DR-TB and DR-TB/HIV co-infected patients are encouraging, they are inconclusive because of the low power of our study. We recommend a prospective study with a larger sample size that would increase the power and therefore the confidence in the results.

Chapter 2.2

INTRODUCTION

Namibia is currently experiencing the dual burden of human immunodeficiency (HIV) infection and HIV-associated tuberculosis (TB). [1] In 2010, the national HIV prevalence among adults aged 15-49 years was 13.5% [2], the TB case notification rate was 589 per 100,000 population, while 56% of TB patients were co-infected with HIV. [3] Of concern is the high prevalence of drug-resistant tuberculosis (DR-TB), with 285 cases reported nationally in 2010. [3] Treatment of DR-TB is difficult and often involves a combination of more than three different types of second-line medicines, [4, 5] some of which are associated with the occurrence of serious adverse events, such as severe hepatic, renal, auditory and vestibular toxicity. [6-9] This problem is compounded in patients concurrently treated for both DR-TB and HIV infection because of the potential overlap of anti-TB and antiretroviral (ARV) drug-related adverse events and drug-drug interactions. [10-12]

Adverse events during DR-TB therapy may complicate patient adherence to treatment schedules [9] and negatively affect treatment outcomes. [12] Severe adverse events were the main reason why 15% of patients on MDR-TB chemotherapy failed to adhere to treatment regimens in a study by Xu *et al.* [13] In another study, up to 64% of MDR-TB patients were compelled to either change, suspend or terminate second-line anti-tuberculosis medications because of the serious adverse events associated with anti-tuberculosis medications. [9] Lorent *et al.* have reported that HIV co-infection was associated with a threefold increase in the risk of serious adverse events in patients treated for all forms of tuberculosis in Rwanda. [14] Therefore, DR-TB chemotherapy, which often lasts for about 18-24 months, requires close clinical monitoring as well as the prevention, minimization and treatment of the possible adverse events. [4, 5] In a previous paper, we showed that adverse effects are common during treatment of DR-TB in Namibia, particularly in the intensive phase of therapy. [15] In the same paper, we also reported that some of the adverse events such as nausea, decreased hearing and joint pain were more prevalent in DR-TB patients co-infected with HIV.

Various patient-related factors are associated with the increased risk of experiencing an adverse event during TB chemotherapy. A study conducted in Canada found the occurrence of any major adverse events of first-line TB therapy to be associated with being female; to being over 60 years of age; to being of Asian descent; and to being HIV-infected. [16] Another study in India found that female gender, disease extent and poor nutritional status were the most important predisposing factors for the hepatotoxicity caused by anti-TB medicines. [17] In addition, Pande, *et al.*

[18] included slow acetylator status as a potential risk factor for isoniazid toxicity. Similar risks factors were identified in other studies. [19-24]

However, relatively little is known about the influence of these and other factors on the risk of adverse drug events in patients treated for drug-resistant TB, especially regarding the influence of HIV infection and antiretroviral therapy. The high prevalence of HIV and DR-TB and the frequent co-infection of HIV and DR-TB in Namibia provided us with a unique opportunity to investigate the influence of HIV co-infection, antiretroviral co-medication and other factors on the risk of frequent, clinically significant adverse events observed during treatment of DR-TB.

Objective

The main objective of the present study was to compare the absolute risks and risk-factors for commonly observed adverse events (occurring in > 20% of patients) during DR-TB treatment in HIV infected and HIV uninfected patients.

METHODS

Study design and population

We conducted a retrospective cohort analysis of all patients treated for DR-TB with individualised second-line anti-tuberculosis regimens at a DR-TB ward between 2008 and 2010. The study population included all the patients who were diagnosed with drug-resistant tuberculosis and were treated with second-line anti-TB medicines at the Kondja TB ward, which is a specialised public sector drug-resistant TB treatment facility in Namibia, in the period between 01 January 2008 and 24 February 2010, both dates being inclusive. Patients were followed from the time they were initiated on second-line anti-tuberculosis medication to the earliest of either occurrence of each of the adverse event of interest, death, loss-to-follow up or study end date. During the follow-up time, all patients diagnosed with any form of tuberculosis were routinely counseled and tested for human immunodeficiency virus (HIV) co-infection and this information was recorded in their medical files. [3] The details of treatment of drug-resistant tuberculosis in this facility have been described elsewhere. [15]

Ethical approval for the study was obtained from the Namibian Ministry of Health and Social Services (MoHSS) research unit, as well as from the University of the Western Cape (UWC) Higher Degrees Committee, both of which are Institutional Review Boards (IRBs). [25] Additional permission was granted by the facility management to anonymously collect the required data from patients' medical files. The need for prior informed consent from the patients was waived, because the study utilized secondary data that had already been collected as part of the patients' routine clinical care at the DR-TB treatment facility.

Data collection

We reviewed patients' treatment charts and collected the required data using a structured data extraction form. The data included patients' age, gender, baseline body weight, HIV status, specific drugs in the individualized DR-TB regimen, antiretroviral therapy regimen, type of Mycobacterium tuberculosis drug-resistance, length of time on DR-TB treatment (intensive phase and continuation phase), documented adverse events, grading of the severity of the adverse events and the time (week) when the adverse events were reported or documented.

During hospitalized care, when the intensive phase of DR-TB therapy was administered, clinicians monitored patients on a daily basis although active surveillance using the adverse event form was conducted on a weekly basis. The observed symptomatic adverse events were recorded on a standard DR-TB drug adverse event monitoring form, developed by the national tuberculosis and leprosy program as part of the patient DR-TB treatment monitoring chart. This form contained eighteen adverse events, namely: abdominal pain, constipation, hearing loss, depression, diarrhea, dizziness, fatigue, fever, headache, joint pain, nausea, neuropathy, psychosis, rash, tinnitus, tremors, vision changes and vomiting. [5]

In the continuation phase of therapy, the patients after being discharged from the DR-TB treatment ward, were placed on a daily directly observed treatment programme that was supervised by a trained community health worker or nurse and were actively screened for adverse events on a monthly basis.

Data analysis

The data were entered into Epi Info, version 3.4.3 (November 2007, Centers for Disease Control and Prevention, Atlanta, USA), for data management and statistical analysis. The accuracy and completeness of the entered data was checked against the original handwritten paper forms. Any errors and discrepancies were investigated and rectified by the principal investigator. Categorical data was coded either as binary or multiple responses to facilitate computerized analysis. Microsoft Excel® (Microsoft office 2010, Microsoft Corporation, Washington State, USA) was subsequently used to draw tables and charts.

We used descriptive statistics to analyze the frequencies and distributions of the various variables studied, including the prevalence of drug exposures and the absolute risks (cumulative incidence) of the observed adverse events. Measures of central tendency and dispersion such as the mean and standard deviation (mean ± SD), and median and inter quartile range (IQR), were used to summarize continuous variables. The non-paired Student's t-test was used to compare the means of normally distributed continuous variables between two groups, for example, comparison of the mean age between male and female patients. The chi square (χ^2), Mantel-Haensel χ^2 or the Fisher

Exact test (if the expected value of a cell was less than 5) were used as appropriate to compare categorical variables and the resulting *p*-values for the statistical comparisons reported.

Specifically, we sought to examine the following factors for their influence on the risk of the commonly occurring clinically significant adverse events: duration of DR-TB treatment; HIV co-infection; antiretroviral co-medication; treatment with specific anti-TB medicines; baseline body weight; gender and age. These risk factors were chosen based on our review of the literature, where similar risk factors have previously been documented. [11, 12, 14, 16, 17, 26] We conducted bivariate analysis using 2 x 2 contingency tables to calculate the risk ratio (RR) of the association of specific risk factor and adverse event pairs at 95% level of confidence, for the overall cohort as well as for the subgroup analysis, stratified by HIV infection status. Although the protocol was to study all the eighteen adverse events that are routinely monitored during DR-TB treatment in Namibia, we couldn't examine risk factors for each of them because of the small absolute counts for some of the adverse events. Instead, we limited risk factor analysis to the four adverse events with a frequency of occurrence of greater than 20%, which had bigger absolute counts to enable 2 x 2 cross-tabulation and stratified statistical analysis. For each of the four adverse events of interest, the overall cohort risk ratios, the stratum-specific risk ratios and the p-values were reported. The overall and stratum-specific risk ratios where compared for effect-modification. In all the analyses, two-sided *p*-values of less than 0.05 were considered to be statistically significant.

RESULTS

A total of 59 patient records were retrieved, two of which had missing data on the patient's HIV status. Of the 57 drug-resistant tuberculosis patients with known HIV status who were included in the analysis, 31 (53%) were co-infected with HIV. In Table 1, the distribution of demographic and clinical characteristics was comparable between HIV infected and HIV uninfected DR-TB patients, except for age, for which HIV infected patients were on average 6.5 years older than HIV uninfected patients (*p*=0.007).

Table 1: Demographic and clinical characteristics of the DR-TB patients by HIV status

	HIV status (N=57)		
	HIV infected (n=31)	HIV uninfected (n=26)	P- value
Gender: Male, n (%)	19 (61%)	17 (65%)	0.41
Age: mean ± SD yrs (range)	37.3 ± 7.6 (21-55)	30.8 ± 10.0 (11-53)	0.007*
Weight: mean ± SD kg (range)	52.7 ± 12.5 (24.2-68.7)	52.2 ± 10.5 (29-92)	0.38
HAART, n (%)	13 (42%)	n/a	-
AZT-based HAART, n (%)	5 (16%)	n/a	-
Previous TB treatment, n (%)	28 (94%)	24 (92%)	0.62
MDR-TB, n (%)	17 (55%)	18 (69%)	-
Polydrug resistant-TB, n (%)	11(35%)	7 (27%)	-
XDR-TB, n (%)	1 (3%)	0 (%)	-
Duration (days): intensive phase therapy; median (IQR)	184 (152-211)	181 (165-243)	-
Number of drugs in intensive phase regimen; median (IQR)	5 (5-6)	5 (5-6)	-
Number of drugs in continuation phase regimen; median (IQR)	3 (3-3)	3 (3-3)	-

SD=standard deviation; yrs=years; kg=kilogrammes; HIV=human immunodeficiency virus; HAART=highly active antiretroviral therapy; TB=tuberculosis; MDR=multidrug resistant; XDR=extensively resistant; IQR=interquartile range

The pattern of treatment of drug-resistant tuberculosis using specific second-line anti-tuberculosis medicines was similar in both HIV infected and HIV uninfected patients. Of note, ethionamide and pyrazinamide were administered in nearly all the DR-TB patients, regardless of their HIV status (Table 2).

Of the 18 studied adverse events, only abdominal pain had a statistically significant greater risk of occurrence in HIV infected patients compared with HIV uninfected patients (26% vs 4%, p = 0.02) as shown in Table 3. In the entire cohort of 57 DR-TB patients, tinnitus (40%), joint pain (26%), hearing loss (23%) and nausea (21%) were the four most commonly observed adverse events, occurring in more than 20% of the patients.

Table 2: Exposure to second-line anti-tuberculosis medicines by HIV status and weight-based dosing protocol

Anti-TB Drug name	Patients exposed, n (%)		Dosing by weight class*			
	HIV infected patients n=31	HIV uninfected patients n=26	<33 KG	33–50 KG	51–70 KG	>70 KG (Maximum dose)
Pyrazinamide	29 (94%)	24 (92%)	30–40 mg/kg daily	1000–1750 mg daily	1750–2000 mg daily	2000–2500 mg daily
Ethionamide	26 (84%)	26 (100%)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Levofloxacin	19 (61%)	18 (69%)	Usual adult dose for MDR-TB is 750 mg	750 mg	750 mg	750–1000 mg
Ethambutol	19 (61%)	16 (62%)	25 mg/kg daily	800–1200 mg daily	1200–1600 mg daily	1600–2000 mg daily
Kanamycin	16 (52%)	14 (54%)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Cycloserine	14 (45%)	13 (50%)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Amikacin	12 (39%)	9 (35%)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Ciprofloxacin	11 (35%)	8 (31%)	20–30 mg/ kg daily	1500 mg 1500 mg	1500 mg	
Rifampicin	7 (23%)	6 (23%)	10–20 mg/kg daily	450–600 mg daily	600 mg daily	600 mg daily
Para-aminosalicylic acid	3 (10%)	2 (8%)	150 mg/kg daily			
Capreomycin	3 (10%)	1 (4%)	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Isoniazid	3 (10%)	1 (4%)	4-mg/kg daily or 8–12 mg, 3 x wk	200–300 mg daily or 450–600 mg, 3 x wk	300 mg daily or 600 mg, 3 x wk	300 mg daily or 600 mg, 3 x wk
Streptomycin	1 (3%)	2 (8%)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Clofazimine	1 (3%)	0 (0%)	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			
Amoxicillin/Clavulanic acid	1 (3%)	0 (0%)	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			

TB=tuberculosis; HIV=human immunodeficiency virus, KG (or kg) =kilogrammes; mg=milligrammes; x=times; wk=week
*Source: WHO, (2006). Guidelines for the programmatic management of drug-resistant tuberculosis: 147–8.

Chapter 2.2

Table 3: Comparison of the risks of occurrence of adverse events by HIV status

Adverse events (18)	Cumulative incidence for cohort n/57 (percent)	HIV infected n/31 (percent)	HIV uninfected n/26 (percent)	P-value
Tinnitus	23 (40%)	12 (39%)	11 (42%)	0.78
Joint pain	15 (26%)	9 (29%)	6 (23%)	0.61
Hearing loss	13 (23%)	8 (26%)	5 (19%)	0.56
Nausea	12 (21%)	8 (26%)	4 (15%)	0.34
Headache	11 (19%)	6 (19%)	5 (19%)	0.99
Fatigue	10 (18%)	4 (13%)	6 (23%)	0.26
Abdominal pain	9 (16%)	8 (26%)	1 (4%)	0.02*
Dizziness	8 (14%)	4 (13%)	4 (15%)	0.54
Rash	7 (12%)	6 (19%)	1 (4%)	0.08
Vomiting	6 (11%)	4 (13%)	2 (8%)	0.42
Diarrhea	5 (9%)	3 (10%)	2 (8%)	0.58
Neuropathy	4 (7%)	2 (6%)	2 (8%)	0.62
Fever	3 (5%)	0 (0%)	3 (12%)	0.09
Vision changes	3 (5%)	1 (3%)	2 (8%)	0.43
Depression	2 (4%)	1 (3%)	1 (4%)	0.71
Psychosis	2 (4%)	1 (3%)	1 (4%)	0.71
Constipation	1 (2%)	1 (3%)	0 (0%)	0.54
Tremors	0 (0%)	0 (0%)	0 (0%)	n/a

HIV=human immunodeficiency virus; *statistically significant; n/a=not applicable; p-value is for Chi square test comparing two proportions

Tinnitus

Overall, 23 out of the 57 patients (40%) complained of tinnitus during the course of DR-TB therapy. Of these 23 patients, 12 were HIV infected and 11 were HIV uninfected. The absolute risk of experiencing tinnitus among HIV infected patients was 12/31 (39%), while the absolute risk was 11/26 (42%) in HIV uninfected patients. There was no statistically significant difference in risk between the two HIV sub-groups (*p*=0.78, Table 3). The specific risk factors for tinnitus were similar in both HIV infected and HIV uninfected patients (Table 4). None of the studied factors emerged as a statistically significant risk factor for tinnitus. We were unable to confirm effect modification in the stratified analysis as the risk ratios were similar for the HIV-infected and the uninfected patients with wide, overlapping confidence intervals.

Table 4: Risk factor analysis for the occurrence of tinnitus, stratified by HIV status

Risk-factors	Overall Cohort of DR-TB patients (n=57)	HIV Infected DR-TB Patients (n=31)	HIV Uninfected DR-TB Patients (n=26)
	RR (95%CI) P-value	Stratum-specific RR, (95%CI) P-value	Stratum-specific RR, (95%CI) P-value
1. Treatment period < 4 weeks	0.8 (0.5-1.5) P=0.38	1.2 (0.5-2.8) P=0.68	0.5 (0.2-1.4) P=0.18
2. Any HAART regimen	1.8 (0.7-5.2) P=0.21	1.8 (0.7-5.2) P=0.21	n/a
3. AZT-based HAART	0.8 (0.2-2.9) P=0.59	0.9 (0.2-2.9) P=0.59	n/a
4. Cycloserine –based DR-TB regimen	1.2 (0.6-2.3) P=0.37	0.9 (0.4-2.1) P=0.76	1.8 (0.7-4.6) P=0.24
5. Amikacin –based DR-TB regimen	1.1 (0.6-2.1) P=0.49	1.1 (0.5-2.8) P=0.54	1.1 (0.4-2.7) P=0.60
6. Female gender	0.8 (0.4-1.6) P=0.34	0.8 (0.3-2.1) P=0.46	0.8 (0.3-2.2) P=0.50
7. Baseline body weight≤45kg	0.6 (0.2-1.7) P=0.22	0.4 (0.1-2.6) P=0.28	0.7 (0.2-2.5) P=0.49
8. Age 30≥years	0.7 (0.4-1.4) P=0.23	0.7 (0.3-1.9) P=0.43	0.7 (0.3-1.8) P=0.47

HIV=human immunodeficiency virus; DR-TB=drug-resistant tuberculosis; HAART=highly active antiretroviral therapy; RR=Risk Ratio; 95% CI= 95% confidence interval; < means less than; ≥ means greater than or equal to; ≤ means less than or equal to; AZT= zidovudine; kg= kilogrammes; P= P value; n/a=not applicable

Hearing loss

Overall, 13 out of the 57 patients (23%) complained of hearing loss. Of these 13 patients, 8/31 (26%) were HIV infected while 5/26 (19%) were HIV uninfected. Statistically, the difference in the absolute risk between the two HIV status groups was not significant (p=0.56, Table 3). The specific risk-factors for this adverse event were similar in both HIV infected and HIV uninfected patients (Table 5). None of the studied factors emerged as a statistically significant risk factor for hearing loss. We were unable to confirm effect modification in the stratified analysis as the risk ratios were similar for the HIV-infected and the uninfected patients with wide, overlapping confidence intervals.

Table 5: Risk factor analysis for the occurrence of hearing loss, stratified by HIV status

Risk-factors	Overall Cohort of DR-TB patients (n=57)	HIV Infected DR-TB Patients (n=31)	HIV Uninfected DR-TB Patients (n=26)
	RR (95%CI) P-value	Stratum-specific RR, (95%CI) P-value	Stratum-specific RR, (95%CI) P-value
1. Treatment period < 4 weeks	0.6 (0.2-1.6) P=0.25	0.5 (0.2-1.7) P=0.24	0.8 (0.2-3.8) P=0.62
2. Any HAART regimen	0.5 (0.1-2.1) P=0.29	0.5 (0.1-2.1) P=0.29	n/a
3. AZT-based HAART	0.0 - P=0.36	0.0 - P=0.36	n/a
4. Cycloserine –based DR-TB regimen	0.7 (0.3-1.9) P=0.34	0.7 (0.2-2.5) P=0.47	0.7 (0.1-3.3) P=0.50
5. Amikacin –based DR-TB regimen	2.0 (0.8-5.2) P=0.13	2.6 (0.8-9.1) P=0.12	1.3 (0.3-6.2) P=0.58
6. Female gender	0.5 (0.2-1.7) P=0.23	0.2 (0.0-1.6) P=0.09	1.4 (0.3-6.9) P=0.52
7. Baseline body weight≤45kg	1.6 (0.6-4.2) P=0.31	2.2 (0.7-6.7) P=0.21	0.8 (0.1-6.1) P=0.68
8. Age 30≥years	1.0 (0.4-2.9) P=0.61	0.7 (0.2-2.7) P=0.50	1.3 (0.3-6.5) P=0.58

HIV=human immunodeficiency virus; DR-TB=drug-resistant tuberculosis; HAART=highly active antiretroviral therapy; RR=Risk Ratio; 95% CI= 95% confidence interval; < means less than; ≥ means greater than or equal to; ≤ means less than or equal to; AZT= zidovudine; kg= kilogrammes; P= P value; n/a=not applicable

Joint pain

In total, there were 15 out of the 57 studied patients (26%) who experienced joint pain. Of these 15 patients, 9/31 (29%), were HIV infected while 6/26 (23%) were HIV uninfected. The difference in the absolute risk of experiencing joint pain among HIV infected patients compared to HIV uninfected patients was not statistically significant (p= 0.61, Table 3).

Although treatment with a cycloserine-based regimen was associated with an increased risk of joint pain in the entire cohort of DR-TB patients (RR= 4.4, 95% CI 1.4-14.1, p=0.004), the risk ratio remained virtually unchanged between the two HIV status groups (RR, HIV infected= 4.3, p=0.03; RR, HIV uninfected= 5, p=0.08) as shown in Table 6. Considering that levofloxacin and pyrazinamide could potentially cause

joint pain, [27] we further conducted an overall cohort bivariate analysis for levofloxacin and pyrazinamide, which revealed that neither levofloxacin nor pyrazinamide was statistically significantly associated with the occurrence of joint pain in our cohort (levofloxacin exposure RR= 1.5, 95% CI 0.5-4.1, p =0.32 and pyrazinamide exposure RR= 1.1, 95% CI 0.2-6.1, p=0.72). In addition, there was an indication of effect modification by HIV exposure for the association between female gender and joint pain. The risk ratio for the stratum of HIV infected patients was more pronounced (RR=3.2, 95% CI 1.0-10.3, p=0.05) compared to that for the HIV uninfected patients (RR=0.4, 95% CI 0.1-3.1, p=0.35).

Table 6: Risk factor analysis for the occurrence of joint pain, stratified by HIV status

Risk-factors	Overall Cohort of DR-TB patients (n=57) RR (95%CI) P-value	HIV Infected DR-TB Patients (n=31) Stratum-specific RR, (95%CI) P-value	HIV Uninfected DR-TB Patients (n=26) Stratum-specific RR, (95%CI) P-value
1. Treatment period < 4 weeks	1.0 (0.4-2.4) P=0.63	1.1 (0.4-3.1) P=0.61	0.8 (0.2-3.8) P=0.62
2. Any HAART regimen	1.2 (0.4-4.0) P=0.53	1.2 (0.4-4.0) P=0.53	n/a
3. AZT-based HAART	0.5 (0.1-3.8) P=0.49	0.5 (0.1-3.8) P=0.48	n/a
4. Cycloserine –based DR-TB regimen	4.4* (1.4-14.1) P=0.004	4.3* (1.04-17.3) P=0.03	5.0 (0.7-37.1) P=0.08
5. Amikacin –based DR-TB regimen	0.4 (0.1-1.3) P=0.10	0.5 (0.1-1.8) P=0.21	0.40 (0.1-2.8) P=0.30
6. Female gender	1.6 (0.7-3.7) P=0.23	3.2 (1.0-10.3) P=0.05	0.4 (0.1-3.1) P=0.35
7. Baseline body weight≤45kg	0.5 (0.1-2.1) P=0.28	1.0 (0.3-3.8) P=0.65	0.0 - P=0.17
8. Age 30≥years	0.9 (0.4-2.3) P=0.55	0.5 (0.2-1.4) P=0.22	1.7 (0.4-7.8) P=0.40

HIV=human immunodeficiency virus; DR-TB=drug-resistant tuberculosis; HAART=highly active antiretroviral therapy; RR=Risk Ratio; 95% CI= 95% confidence interval; < means less than; ≥ means greater than or equal to; ≤ means less than or equal to; AZT= zidovudine; kg= kilogrammes; P= P value; n/a=not applicable; * means statistically significant

Nausea

In total, 12 out of the 57 studied patients (21%) experienced nausea. Of these 12 patients, 8/31 (26%) were HIV infected and 4/26 (15%) were HIV uninfected, with no statistically significant difference in the risks between the two sub-groups (*p*=0.34) as shown in Table 3. We found none of the risk factors to be statistically significantly associated with the occurrence of nausea (Table 7). In addition, there was an indication of effect modification by HIV exposure for the association between the time (in weeks) on treatment and the occurrence of nausea. The relationship was more pronounced among HIV infected patients (RR=5.1, 95% CI 0.7-36.9, *p*=0.06), compared to the HIV uninfected patients (RR=0.4, 95% CI 0.1-3.3, *p*=0.38).

Table 7: Risk factor analysis for the occurrence of nausea, stratified by HIV status

Risk-factors	Overall Cohort of DR-TB patients (n=57) RR (95%CI) P-value	HIV Infected DR-TB Patients (n=31) Stratum-specific RR, (95%CI) P-value	HIV Uninfected DR-TB Patients (n=26) Stratum-specific RR, (95%CI) P-value
1. Treatment period < 4 weeks	1.8 (0.6-5.1) P=0.24	5.1 (0.7-36.9) P=0.06	0.4 (0.1-3.3) P=0.38
2. Any HAART regimen	1.6 (0.4-6.1) P=0.37	1.6 (0.4-6.1) P=0.37	n/a
3. AZT-based HAART	4.8 (0.7-34.4) P=0.12	4.8 (0.7-34.4) P=0.12	n/a
4. Cycloserine –based DR-TB regimen	3.3 (1.0-11.1) P=0.03	2.0 (0.6-7.0) P=0.23	- - P=0.05
5. Amikacin –based DR-TB regimen	0.9 (0.3-2.5) P=0.53	0.5 (0.1-2.2) P=0.31	1.8 (0.3-11.3) P=0.43
6. Female gender	0.4 (0.1-1.7) P=0.16	0.5 (0.1-2.2) P=0.31	0.0 - P=0.30
7. Baseline body weight≤45kg	1.2 (0.4-3.6) P=0.53	2.2 (0.7-6.7) P=0.21	0.00 - P=0.32
8. Age 30≥years	0.9 (0.3-2.7) P=0.57	1.7 (0.3-11.2) P=0.50	0.3 (0.0-2.4) P=0.24

HIV=human immunodeficiency virus; DR-TB=drug-resistant tuberculosis; HAART=highly active antiretroviral therapy; RR=Risk Ratio; 95% CI= 95% confidence interval; < means less than; ≥ means greater than or equal to; ≤ means less than or equal to; AZT= zidovudine; kg= kilogrammes; *P*= P value; n/a=not applicable

DISCUSSION

To the best of our knowledge, this is the first ever documented study in Namibia that compares by HIV infection status the risks and risk factors for the occurrence of adverse events among patients treated for DR-TB. The 57 patients treated for DR-TB in our cohort had similar demographic and clinical characteristics as well as a similar profile of exposure to specific DR-TB medicines when compared by HIV status, except for age. On average, HIV infected patients were slightly older than HIV uninfected patients. Except for abdominal pain, there were no statistically significant differences in the risk of adverse event occurrence between HIV infected and HIV uninfected patients. The risk ratios for the association between treatment with a cycloserine-based DR-TB regimen and the occurrence of joint pain were not much different between HIV infected and HIV uninfected patient groups.

We report that patients included in our cohort were generally young adults in their 30s, which precluded us from examining the influence of either very young age or of advanced age on the occurrence of adverse events. Several studies on DR-TB treatment that have been conducted in low and middle income countries have also reported such young adult patient profiles. [7, 8, 11, 14]

The treatment of DR-TB in our cohort was in accordance with the standard treatment guidelines recommended by Namibia's Ministry of Health and Social Services. [5] Generally, the types of drugs used in DR-TB treatment regimens in our setting were similar to those used in other settings, although the prevalence of use of specific second-line anti-tuberculosis medicines belonging to a particular therapeutic group may have been different. For instance, taking the case of aminoglycosides and capreomycin, most of the patients in our study were treated with either kanamycin (54%) or amikacin (36%), with very few (7%) being treated with capreomycin. In the study by Isaakidis *et al.* conducted in India, the patients in their cohort were treated with either kanamycin (57%) or capreomycin (57%) but not amikacin. [11] Similarly, in the study conducted in Turkey by Torun and colleagues, amikacin was administered in about 80% of the patients, capreomycin in 8% and kanamycin in 5%. [7] In another study reported from Russia by Shin *et al.*, patients in their cohort were treated with either capreomycin (63%) or kanamycin (47%) with only 0.8% of the patients treated with amikacin. [8] Such differences in the usage patterns of specific second-line anti-tuberculosis medicines may explain differences in the frequency and the magnitude of the risk of occurrence of specific adverse events across settings.

The risk of abdominal pain was significantly greater in HIV infected patients than in HIV uninfected patients. This finding is consistent with that reported by Isaakidis *et al.* who found that, overall, gastrointestinal symptoms were the most common adverse event in their cohort of HIV co-infected patients. [11] This may have arisen because of

overlapping gastrointestinal discomfort due to concomitant anti-TB and antiretroviral medication. [10]

We found that the absolute risks of tinnitus or hearing loss among HIV infected patients was 39% and 26% respectively, while in HIV uninfected patients, it was 42% and 19% respectively. Comparable findings have been reported from other cohorts in which patients were predominantly treated with ototoxic injectable drugs in their DR-TB regimens. For example, Torun and colleagues studied a cohort of 263 HIV uninfected patients treated for MDR-TB in Turkey using either amikacin- or kanamycin-based regimens and found that 42% of the patients experienced ototoxicity. [7] In a Southern African cohort of 76 MDR-TB patients with a high (74%) prevalence of HIV co-infection, the risk of ototoxicity was 36% [26] .In Tomsk, Russia in a cohort of 244 MDR-TB patients predominantly treated with capreomycin-based regimens, the risk of ototoxicity was much lower, at 16%. [8] The risk of ototoxicity in a cohort of 67 HIV and MDR-TB co-infected patients in Mumbai, India, who were treated with MDR-TB regimens that contained either capreomycin or kanamycin but not amikacin was also low (10%). [11] The variation in reported risks of ototoxicity across settings may have been due to inherent differences in the cochleotoxic potential of amikacin, kanamycin and capreomycin. Although not explicitly reported in the literature, it appears that amikacin has the greatest predisposition for causing auditory loss as compared to kanamycin, while capreomycin has the least tendency. [6-9, 26, 28-33] These differences across practice settings may also arise from differences in the choice and use of these injectable second-line anti-TB drugs in tuberculosis treatment guidelines and also in variation in the intensity of clinical screening and audiological monitoring in patients treated with these drugs. [29, 32, 33]

We found no evidence of differences in the absolute risks of tinnitus or hearing loss between HIV infected and HIV uninfected patients in our study. Similarly, we were unable to find distinct risk factors for tinnitus or hearing loss in either group of patients. This could have been due to the comparable prevalence of use of specific cochleotoxic anti-tuberculosis (aminoglycosides) and similarity in other characteristics between both groups, which may have attenuated the magnitude of the association between risk factors and ototoxicity. It would, therefore, require a study with a larger sample size to clarify the relationship between risk factors and the auditory damage that is associated with the use of injectable anti-tuberculosis medicines.

In addition, we found that the absolute risk of joint pain among HIV infected patients was 29%, while in HIV uninfected patients, it was 23%. There is a wide variation in the risk of joint pain reported in the literature. For instance, Shin and colleagues have reported a higher risk (47%) of joint pain (arthralgia) in a Russian cohort of MDR-TB patients, [8] while Bloss *et al.* reported a lower risk (13%) in a cohort of 1,027 patients in Latvia. [9] A similar low risk (11%) of joint pain among HIV uninfected patients was

reported by Torun and colleagues. [7] In the Philippines, Tupasi *et al.* reported a risk of 31% for minor joint pain and 17% for arthritis/ gout. [34] This variation could be partly attributed to differences in the definition of joint pain and the grading of severity that was utilized across the settings.

Our finding that treatment of drug-resistant tuberculosis using cycloserine-containing regimens is associated with the occurrence of joint pain is novel and has not been previously reported in the literature. However, the association of pyrazinamide and joint pain (arthralgia) is well established and has been extensively reported in the literature. [27] It is notable that almost all (98%) of the 57 patients in the studied sample were treated with pyrazinamide-containing DR-TB regimens, meaning that exposure to pyrazinamide was essentially common to all patients included in this study. Therefore, any differences in the risk of joint pain can only be attributed to other drugs contained in the regimen other than pyrazinamide. In this cohort, neither the use of levofloxacin nor pyrazinamide containing regimens were statistically significant risk factors for the occurrence of joint pain.

We did not find any statistically significant difference in the risk of nausea between HIV infected and HIV uninfected patients. This finding is contrary to expectation, given that nausea is common during the use of zidovudine (AZT). [35] Failure to detect a statistically significant difference between the two HIV subgroups may have been due to the low power of our study.

In some instances, HIV status appeared to modify the effect of the association of some of the risk factors and adverse event occurrence, but the wide and overlapping confidence intervals are inconclusive. Therefore we would like to exercise caution in interpreting findings of the exploration of effect modification in this study.

Our study has several limitations. The small sample size and the retrospective nature of the study are its biggest limitation. Specifically, the risk ratios in Tables 4-7 are quite wide, largely because of the low counts within each cell of the contingency tables. Due to the retrospective design, HIV treatment-related adverse events were not included because they were not routinely captured on the TB treatment records maintained by the TB clinic. Furthermore, data on the severity grading and time-to-event for each of the adverse events were incomplete, which precluded the use of time-varying analyses for each adverse event. Lastly, the data collected in this study were largely based on subjective reporting of symptoms by patients, which may have underestimated or overestimated the true frequency of occurrence of the adverse events.

Despite the above limitations, the study has yielded important information to guide implementation of the programmatic management of drug-resistant tuberculosis in Namibia. The implication of the findings of this study for clinical practice is the continued need for extra vigilance in monitoring of adverse events in patients concomitantly treated for drug-resistant tuberculosis and HIV infection. The documentation of the

occurrence and clinical management of adverse events in the patient DR-TB treatment records should be as complete as possible, including those associated with concomitant antiretroviral therapy. In terms of policy and treatment guidelines, the Namibian National Tuberculosis and Leprosy Programme should continue strengthening pharmacovigilance systems especially among patients with DR-TB/HIV co-infection and other major co-morbidities so that specific drug therapy-related risks and risk factors could be better understood. Adherence to the tuberculosis treatment guidelines by clinicians should be reinforced.

CONCLUSIONS

Generally, the absolute risks and risk factors for adverse events were similar between HIV infected and HIV uninfected patients treated for drug-resistant tuberculosis in our Namibian sample of 57 patients. In some instances, HIV exposure appeared to modify the effects of the risk factors on the four common adverse events that we examined. Although our findings of comparable adverse event risks between DR-TB and DR-TB/HIV co-infected patients are encouraging, they are inconclusive because of the low power of our study. We recommend a prospective study with a larger sample size that would increase the power and therefore the confidence in the results.

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REFERENCES

1. Ministry of Health and Social Services (MoHSS). *National Tuberculosis and Leprosy Programme: Second Medium Term Strategic Plan for Tuberculosis and Leprosy, 2010-2015*. Windhoek: MoHSS; 2010.

2. Ministry of Health and Social Services (MoHSS). *2011/12 Estimates and Projections of the Impact of HIV and AIDS in Namibia*. Windhoek: MoHSS; October 2012.

3. Ministry of Health and Social Services. *National Tuberculosis and Leprosy Programme annual report: 2011-2012*. Windhoek: MoHSS; 2012.

4. World Health Organization (WHO). *Treatment of tuberculosis*, 4th ed. WHO/HTM/TB/2009.420. Geneva: WHO; 2010.

5. Ministry of Health and Social Services (MoHSS). *National Guidelines for the Management of Tuberculosis, Second edition*. Windhoek: MoHSS; March 2006.

6. Nathanson E, Gupta R, Huamani P, *et al.* Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis* 2005; 9: 1027-33.

7. Törün T, Güngör G, Özmen I, *et al.* Side effects associated with the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; 9: 1373-7.

8. Shin SS, Pasechnikov AD, Gelmanova IY, *et al.* Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *Int J Tuberc Lung Dis* 2007; 11: 1314-20.

9. Bloss E, Kukša L, Holtz TH, *et al.* Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. *Int J Tuberc Lung Dis* 2010; 14: 275-81.

10. Venkatesh KK, Swaminathan S, Andrews JR, *et al.* Tuberculosis and HIV Co-infection: Screening and Treatment Strategies. *Drugs* 2011; 71 (9): 1133-1152.

11. Isaakidis P, Varghese B, Mansoor H, , *et al.* Adverse Events among HIV/MDR-TB Co-Infected Patients Receiving Antiretroviral and Second Line Anti-TB Treatment in Mumbai, India. *PLoS One* 2012; 7(7): e40781. doi:10.1371/journal.pone.0040781.

12. Marks DJB, Dheda K, Dawson R, *et al.* Adverse events to antituberculosis therapy: influence of HIV and antiretroviral drugs. *International Journal of STD and AIDS* 2009; 20 (5): 339-345.

13. Xu W, Lu W, ZhouY, *et al.* Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study. *BMC Health Services Research* 2009; 9:168.

14. Lorent N, Sebatunzi O, Mukeshimana G, *et al.* Incidence and Risk Factors of Serious Adverse Events during Antituberculous Treatment in Rwanda: A Prospective Cohort Study. *PLoS One* 2011; 6 (5): e19566. doi:10.1371/journal.pone.0019566

15. Sagwa E, Mantel-Teeuwisse A, Ruswa N, *et al.* The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. *Southern Med Review* 2012; 5 (1): 6-13.

16. Yee D, Valiquette C, Pelletier M, *et al.* Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2003; 167: 1472-1477.

17. Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. *Ann Pharmacother* 2004 [Online] http://www.theannals.com/cgi/content/full/38/6/1074 . [Accessed on 23/06/09 at 12h35].

18. Pande JN, Singh SPN, Khilnani GC, *et al.* Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; 51 (2): 132-136.

Chapter 2.2

19. Nahar BL, Mosharrof Hossain AKM, Islam MM, *et al.* A comparative study on the adverse effects of two anti-tuberculosis drugs regimen in initial two-month treatment period. *Bangladesh J Pharmacol* 2006; 1: 51-7.

20. Furin JJ, Mitnick CD, Shin SS, *et al.* Ocurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. *Int J tuberc Lung Dis* 2001; 5: 648-55.

21. Chhetri AK, Saha A, Verma SC, *et al.* A study of adverse drug reactions caused by first line anti-tubercular drugs in Directly Observed Treatment, Short Course (DOTS) therapy in western Nepal, Pokhara. *Journal of Pakistan Medical Association,* 2008; 58 (10): 531-36.

22. Kishore PV, Subish P, Pradip O, *et al.* Pattern of adverse drug reactions experienced by tuberculosis patients in a tertiary care teaching hospital in western Nepal. *Pakistan Journal of Pharmaceutical Sciences* 2008; 21 (1): 51-6.

23. Gholami K, Kamali E, Hajiabdolbaghi M, *et al.* Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. *Pharmacy Practice* 2006; 4 (3): 134-8.

24. Mehta U, Durrheim DN, Blockman M, *et al.* Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. *British Journal of Clinical Pharmacology* 2007; 65 (3): 396-406.

25. Sagwa, E. 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. Unpublished Master of Public Health thesis, Cape Town, South Africa; University of the Western Cape: February 2012.

26. Seung KJ, Omatayo DB, Keshavjee S, *et al.* Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. *Plos One* 2009; 4: e7186. doi: 10.1371/journal.pone.0007186.

27. Papastavros T, Dolovich LR, Holbrook A, *et al.* Adverse events associated with pyrazinamide and levofloxacin in the treatment of multidrug-resistant tuberculosis. *CMAJ* 2002; 167: 131-6.

28. de Jager P and van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *Int J Tuberc Lung Dis* 2002; 6: 622-7.

29. Duggal P and Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. *BMC Ear, Nose and Throat Disorders* 2007; 7: doi: 10.1186/1472-6815-7-5.

30. Brummett RE and Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrobial Agents and Chemotherapy* 1989; 33:797-800.

31. Nadol JB. Medical progress: Hearing loss. *N Engl J Med* 1993; 329: 1092-1102.

32. Selimoglu E. Aminoglycoside-induced ototoxicity. *Current Pharmaceutical Design* 2007; 13: 119-26.

33. Sturdy A, Goodman A, Jose RJ, *et al.* Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. *J Antimicrob Chemother* 2011; 66: 1815-1820.

34. Tupasi TE, Gupta R, Quelapio MID, *et al.* Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: A cohort study in the Philippines. *Plos One* 2006; 3: e352.

35. Carr A and Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; 356: 1423-30.

Chapter 2.3

Occurrence and clinical management of moderate-to-severe adverse events during drug-resistant tuberculosis treatment: a retrospective cohort study

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ABSTRACT

Objectives: To determine the incidence of symptomatic moderate-to-severe adverse events during treatment of drug-resistant tuberculosis, and to compare their risk and outcomes by patients' human immunodeficiency virus (HIV) co-infection status.

Methods: We conducted a retrospective cohort analysis of patients treated for drug-resistant tuberculosis between January 2008 and February 2010. Routinely, clinicians monitored and managed patients' response to treatment until its completion. Any symptomatic adverse event observed by the clinician or reported by the patient was recorded in the standard patient treatment booklet of the National Tuberculosis and Leprosy Programme. There were 18 symptomatic adverse events routinely monitored. Depending on the nature of the intervention needed, each was graded as mild, moderate or severe. Data were extracted from the patient treatment booklet using a structured form, then descriptive, bivariate and Cox proportional hazard analysis performed, stratified by patients' HIV infection status. Statistical associations were done at the 5% level of significance and reported with 95% confidence intervals.

Results: Fifty seven (57) patients with drug-resistant tuberculosis were identified, 31 (53%) of whom were HIV co-infected. The cumulative incidence of moderate-to-severe adverse events was 46 events in 100 patients. HIV co-infected patients experienced more moderate-to-severe adverse events compared with the HIV uninfected patients (median 3 versus 1 events, p=0.01). They had a four-fold increase in the cumulative hazard of moderate-to-severe adverse events compared with the HIV uninfected patients (HR=4.0, 95% CI 1.5 – 10.5). Moderate-to-severe adverse events were the main determinant of a clinician's decision to reduce the dose or to stop the suspected offending medicine (RR=3.8, 95% 1.2-11.8).

Conclusions: Moderate-to-severe adverse events are common during drug-resistant tuberculosis therapy. They were more likely to occur and to persist in HIV co-infected patients than in HIV uninfected patients. Clinicians should employ various strategies for preventing drug-induced patient discomfort and harm, such as reducing the dose or stopping the suspected offending medicine. Managers of tuberculosis control programmes should strengthen pharmacovigilance systems. We recommend a more powered study for conclusive risk-factor analysis.

INTRODUCTION

The burden of tuberculosis (TB) disease in Namibia remains high, with a case notification rate of 545 cases per 100,000 population in 2012. [1] The prevalence of drug-resistant tuberculosis (DR-TB) in the country, estimated at 20.1 cases per 100,000 TB patients, combined with the high human immunodeficiency virus (HIV) co-infection rate of about 50%, is a major public health concern for the National Tuberculosis and Leprosy Program (NTLP). [1]

Both DR-TB and HIV infections need to be treated, otherwise, the patient may not survive for too long. [2, 3] The adverse effects of second-line anti-tuberculosis and antiretroviral medicines pose a unique challenge in the combined treatment of the two infections. [2,3] Moderate-to-severe adverse events can cause patients' intolerance to second-line anti-tuberculosis medicines and antiretroviral medicines, possibly compromising DR-TB and HIV treatment outcomes. Such intolerance may require the clinician treating the patient to make specific medicine dosage adjustments, regimen changes or stop the treatment. [4,5] Similarly, treatment of HIV with highly active antiretroviral therapy (HAART) is associated with various adverse effects, some of which may overlap with those of second-line anti-tuberculosis medicines. [2,3,6]

This paper is the third and last of a series of papers [7,8] that we have published based on a dataset on the occurrence of adverse events during treatment of DR-TB in Namibia, each paper addressing a different aspect of the adverse events epidemiology. The first paper described the burden of adverse events during treatment of DR-TB, [7] while the second paper compared, by HIV co-infection status, the risks and the risk-factors for the commonly observed adverse events. [8] Apart from our research highlighted above, there is limited scientific literature on the incidence, clinical management and the outcomes of moderate-to-severe adverse events among patients on DR-TB therapy in Namibia.

In this paper, we describe the cumulative incidence and the actions taken by clinicians to manage the moderate-to-severe adverse events occurring during DR-TB treatment. Secondly, we compare the risk and outcomes of these moderate-to-severe adverse events, by patients' HIV co-infection status.

METHODS

Study design

This was a retrospective observational cohort study of consecutive patients treated for DR-TB between January 2008 and February 2010 at the Kondja DR-TB treatment ward in the Walvis Bay District of Namibia. All the DR-TB patients treated at this facility during the specified period were included in the study.

Setting

The study was conducted at the Kondja DR-TB treatment ward, which is a 25-bed district hospital DR-TB treatment facility serving the entire Erongo region of Namibia. The Erongo region had the second largest number of patients on DR-TB treatment in Namibia at the time of the study. In this ward, patients with microbiologically confirmed DR-TB infection were placed on second-line intensive phase treatment that included parenteral amikacin, kanamycin or capreomycin for a minimum of four months, until two sputum smears and two successive cultures turned negative. [7, 9] Clinicians designed individualized regimens and calculated daily doses of each medicine based on patients' body weight, in accordance with the national TB treatment guidelines published in 2006. [9] The HIV co-infected patients were, additionally, treated with HAART regimens that comprised of lamivudine in combination with either zidovudine (AZT) or stavudine (d4T) and efavirenz (EFV) or nevirapine (NVP). [9]

The susceptibility of M. tuberculosis to anti-TB medicines was tested by the Namibia Institute of Pathology using the liquid culture MGIT 960 system (BACTEC™ MGIT™ 960 Mycobacteria Culture System, Becton Dickinson, New Jersey, USA) on all M. tuberculosis confirmed cultures, for susceptibility to isoniazid, rifampicin, streptomycin and etham-butol. All isolates of M. tuberculosis found to be resistant to rifampicin or isoniazid were sent to the National Health Laboratory Service in South Africa for testing of resistance to kanamycin, capreomycin, amikacin, ciprofloxacin, levofloxacin and ethionamide.

Routinely, during DR-TB treatment, patients were closely monitored and supervised by the clinician until completion of treatment. Any clinician-observed or patient-reported symptomatic adverse events were recorded in the standard patient treatment booklet designed by the NTLP. At the time of the study, the DR-TB patient treatment booklet listed 18 symptomatic adverse events that were routinely monitored during treatment: abdominal pain, constipation, hearing loss (decreased hearing), depression, diarrhoea, dizziness, fatigue, fever, headache, joint pain, nausea, neuropathy, psychosis, rash, tin-nitus, tremors, vision changes and vomiting. [9] According to the DR-TB patient treatment booklet, the severity of an adverse event could be classified into three grades. Grade 1 were the mild adverse events, requiring no medical intervention; Grade 2 were the moderate adverse events, requiring palliative [or adjunctive] intervention; while Grade 3 were the severe adverse events, requiring a change in treatment or its discontinuation. [9] Each observed adverse event was graded by the attending clinician as mild, moderate or severe as explained above and was managed according to the severity grading.

Ethical considerations

Ethical approval of the study protocol was obtained from the research unit of the Ministry of Health and Social Services of Namibia (MoHSS) – Ref 17/3/3/AP and the Higher

Degrees Committee of the University of the Western Cape, South Africa, both of which are institutional review boards.

Data collection

The lead researcher collected data from patients' DR-TB treatment booklet using a structured form. No personal identifiers were recorded, to maintain the anonymity and the confidentiality of the patients. The primary study outcome was the occurrence of any adverse event during DR-TB treatment. The secondary outcome was the occurrence of moderate-to-severe adverse events. Further, detailed characterization of each moderate-to-severe adverse event was conducted, which included: its description, time-to-onset, severity grading, duration, actions taken to manage the adverse event, and the outcome of the adverse event.

Definition of terms

In this study, DR-TB included both poly- and multidrug resistant forms of M. tuberculosis. Poly drug-resistance was defined as the resistance of M. tuberculosis to either isoniazid or rifampicin and other first-line anti-tuberculosis medicines, while multidrug resistance was the resistance to at least both isoniazid and rifampicin. [9]

Data analysis

We limited our statistical analyses to descriptive and univariate analysis, due to the small sample of DR-TB patients that was realized. We couldn't perform multivariable analyses because of the few degrees of freedom of the small sample. We therefore calculated absolute and relative frequency counts, measures of central tendency (mean and median) and measures of dispersion including range, interquartile range and standard deviation. We applied two-tailed Student's T-tests to compare group differences in age and weight after testing for normality. For non-normally distributed variables such as the number of adverse events observed, comparisons were made by the non-parametric Mann-Whitney/ Wilcoxon two sample test. We compared proportions and categorical variables using the Chi-square or Fisher exact test respectively, depending on whether or not the expected value for a cell in the cross-tabulation was greater than five.

Associations between exposure and outcome variables were assessed using 2x2 contingency tables, with further stratification by HIV infection status. In addition, Kaplan-Meier and Cox proportional hazard analysis were performed to generate hazard ratios. All the analyses were done in Epi Info 3.4.3. (November 2007, Centers for Disease Control and Prevention, Atlanta, USA) and reported as point estimates, 95% confidence intervals (95% CI) and *p*-values. However, the Kaplan-Meier plot was drawn using the Statistical Package for the Social Sciences (SPSS®) for Windows, version 12.0.1 (IBM Corporation, New York, USA). A p-value of less than 0.05 was considered

to be statistically significant. Lastly, we used Microsoft Excel® (Microsoft office 2010, Microsoft Corporation, Redmond, Washington State, USA) to draw charts and tables.

RESULTS

The proportion of DR-TB patients who experienced any adverse event was 51/57 (89%). Of these 51 patients, 26 (51%) experienced at least one moderate-to-severe adverse event. A medical intervention was made to manage the adverse event in 29 (57%) of the patients. These medical interventions included reducing the medicine dose or stopping the suspected offending medicine in 15 patients (29%), using other adjunctive medicines to treat the adverse event(s) in 14 patients (27%), or completely changing the DR-TB treatment regimen in 9 patients (18%). There were 20/51 (39%) patients who experienced persistent adverse events that lasted for three months or more, while 15/51 (29%) patients were yet to recover from their adverse events by the study end date (Figure 1).
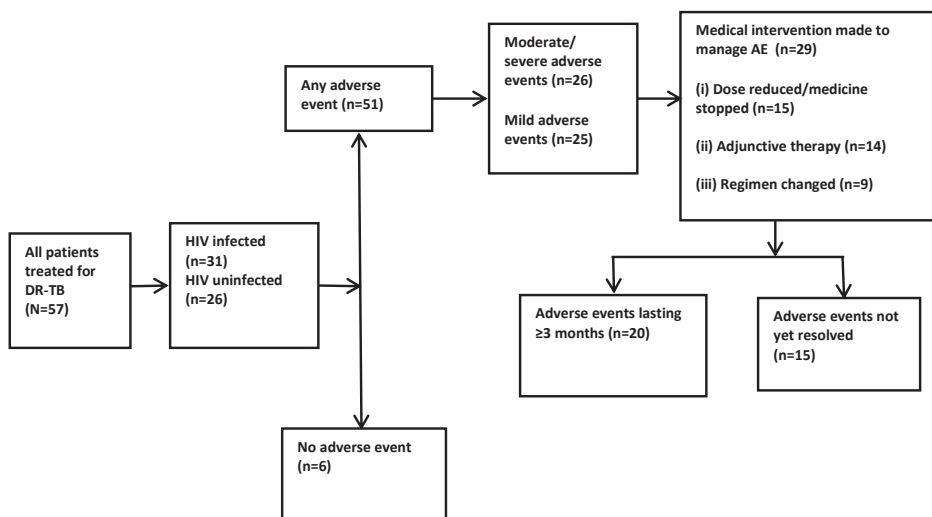
Figure 1: Flow diagram of DR-TB treatment, occurrence and outcomes of adverse events
Legend: DR-TB=drug resistant tuberculosis; HIV=Human immunodeficiency virus; AE=adverse event

The distribution of the patients' demographic and clinical characteristics was generally similar between the 26 DR-TB patients who experienced at least one moderate-to-severe adverse event compared to the 25 who experienced at least one mild adverse event (Table 1). However, the HIV co-infection rate was notably higher among the patients who experienced at least one moderate-to-severe adverse event, compared with those who experienced only mild adverse events (69.2% versus 40%, *p*=0.04).

Table 1: Demographic and clinical characteristics of the patients, by adverse event severity grading

Characteristic	Adverse events by severity grading (N=51)		
	Moderate-to-severe events (n=26)	Mild events (n=25)	P- value
Gender: Male, n (%)	16 (61.5%)	15 (60.0%)	0.91
Age: mean ± SD, yrs	34.1 ± 8.3	35.0 ± 10.2	0.71
Weight: mean ± SD, kg	51.4 ± 10.3	53.9 ± 12.3	0.45
HIV co- infection, n (%)	18 (69.2%)	10 (40%)	0.04
HAART, n (%)	5 (19.2%)	7 (28%)	0.46
Duration (days) of therapy; median (IQR)	183.5 (173-243)	185 (175.5-212)	0.81
Number of drugs in intensive phase regimen; median (IQR)	5 (5-6)	5 (5-6)	0.61

SD=standard deviation; yrs=years; kg=kilogrammes; HIV=human immunodeficiency virus; HAART=highly active antiretroviral therapy; TB=tuberculosis; IQR=interquartile range

Overall, the DR-TB patients co-infected with HIV experienced more moderate-to-severe adverse events compared with the HIV uninfected patients, with a median of 3 adverse events versus 1 adverse event respectively (p=0.01), as depicted in Table 2. Eighteen of the 26 DR-TB patients who experienced at least one moderate-to-severe adverse event (69%), were HIV co-infected (Figure 2).
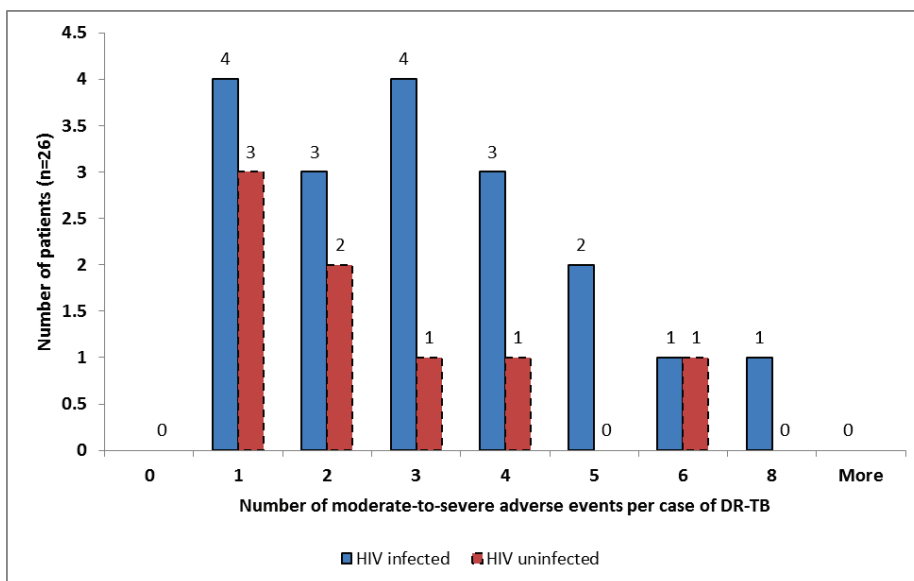
Figure 2: Distribution of the number of moderate-to-severe adverse events by HIV infection status
Legend: DR-TB=drug resistant tuberculosis

Table 2: Frequency of moderate-to-severe adverse events by HIV infection status

Adverse events	Frequency of moderate-to-severe adverse events	
	HIV infected	HIV uninfected
Tinnitus	9	6
Joint pain	7	0
Decreased hearing	8	4
Nausea	5	1
Headache	3	1
Fatigue	5	1
Abdominal pain	5	1
Dizziness	3	0
Rash	3	0
Vomiting	3	0
Diarrhea	2	1
Neuropathy	2	1
Fever	0	0
Vision changes	0	2
Depression	1	0
Psychosis	1	1
Tremors	1	1
Constipation	0	0
Total number of adverse events	**58**	**20**
Median number of adverse events	**3**	**1**
Difference in median (3-1) = 2	*p*=0.01 (Mann-Whitney/Wilcoxon Two-Sample Test)	

The cumulative incidence of moderate-to-severe adverse events in the entire cohort was 26 events out of 57 patients (46 events in 100 patients). By comparison, the cumulative incidence of moderate-to-severe adverse events amongst the HIV co-infected patients was 18 events out of 28 patients (64 events in 100 patients) while it was 8 events out of 23 patients (35 events in 100 patients) amongst the HIV uninfected patients, (*p*=0.04).

In a time-to-event analysis using a Kaplan Meier curve and Cox proportional hazards analysis, the DR-TB patients who were co-infected with HIV had a four-fold cumulative hazard of experiencing moderate-to-severe adverse events compared with the HIV uninfected patients (HR=4.0, 95% CI 1.5 – 10.5, *p*=0.006), Figure 3.
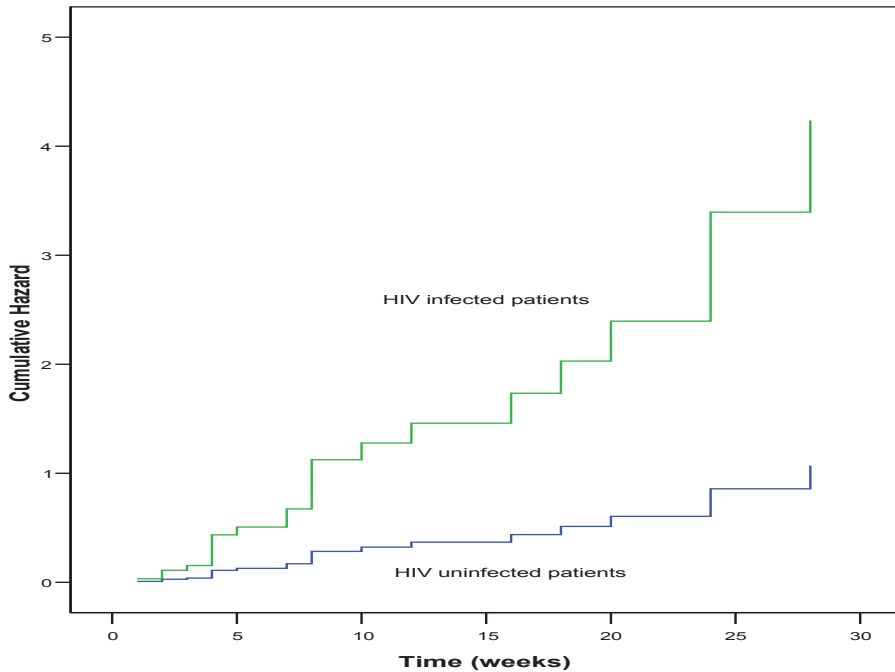
Figure 3: Kaplan Meier curve of the time to the occurrence of moderate-severe adverse events, by HIV status

Legend: HIV=Human immunodeficiency virus

In terms of medicines exposure, the DR-TB patients in our cohort were treated with individualized regimens, based on the susceptibility of the M. tuberculosis to specific second-line anti-TB medicines. In total, the patients were treated with 15 different second-line anti-TB medicines, while the HIV infected patients were additionally treated with HAART regimens, which consisted of lamivudine in combination with either zidovudine (AZT) or stavudine (d4T) and efavirenz (EFV) or nevirapine (NVP). None of the second-line anti-TB or antiretroviral medicines was statistically significantly associated with the occurrence of moderate-to-severe adverse events (Table 3). However, amikacin, ciprofloxacin and ethambutol tended to have a much higher risk when compared with the other second-line anti-TB medicines.

Table 3: Use of specific second-line anti-TB or antiretroviral medicines and the risk of moderate-to-severe adverse events

Anti-TB Medicine	Number (%) treated with the medicine, N=57	Univariate Risk Ratios	95% Confidence Interval	*p*-value
Amikacin	21 (36.8%)	1.5	0.8 – 2.6	0.18
Amoxicillin/ Clavulanate	1 (1.8%)	0.0	-	0.36
Capreomycin	4 (7%)	1.1	0.4 – 3.1	0.86
Ciprofloxacin	19 (33.3%)	1.5	0.8 – 2.5	0.19
Clofazimine	1 (1.8%)	0	-	0.36
Cycloserine	27 (47.4%)	0.8	0.5 – 1.5	0.49
Ethambutol	35 (61.4%)	1.7	0.9 – 3.4	0.10
Ethionamide	52 (91.2%)	0.7	0.3 – 1.6	0.50
Isoniazid	4 (7%)	1.1	0.4 – 3.1	0.86
Kanamycin	30 (52.6%)	0.8	0.4 – 1.4	0.37
Levofloxacin	37 (64.9%)	0.6	0.4 – 1.1	0.11
Para aminosalicylic acid (PAS)	5 (8.8%)	1.4	0.6 – 2.9	0.50
Pyrazinamide	53 (93%)	0.9	0.3 – 2.5	0.86
Rifampicin	13 (22.8%)	0.8	0.4 – 1.7	0.56
Streptomycin	3 (5.3%)	0.7	0.1 – 3.6	0.66
Any HAART regimen	13 (22.8%)	0.8	0.4 – 1.7	0.56
Zidovudine (AZT)	5 (8.8%)	0.4	0.1 – 2.5	0.23
Stavudine (d4T)	6 (10.5%)	1.1	0.5 – 2.6	0.82
Efavirenz (EFV)	10 (17.5%)	0.9	0.4 – 1.9	0.70
Nevirapine (NVP)	3 (5.3%)	0.7	0.1 – 3.7	0.66

We further explored the association between the occurrence of moderate-to-severe adverse events, the specific medical interventions made to manage them and their specific outcomes. From a univariate analysis on the entire cohort, we found that moderate-to-severe adverse events determined whether the clinician chose to reduce the dose or to stop a specific DR-TB medicine, the risk ratio (RR) for the association being 3.8 (95% CI 1.2-11.8, *p*=0.01). Upon stratification to assess for confounding or effect modification by HIV infection status, the association remained similar between HIV infected and HIV uninfected patients (RR=4.2 and RR=4.1 respectively) (Table 4).

Table 4: Relationship between occurrence of moderate-to-severe AEs, medical actions to manage the AEs and their outcome

Medical actions taken to manage AEs and outcome of AEs	Entire cohort analysis	Stratified analysis	
		HIV positive stratum	HIV negative stratum
Dose reduced or medicine stopped	3.8 (1.2-11.8) p=0.007	4.2 (0.6-28.8) p=0.09	4.1 (1.02-16.2) p=0.04
Adjunctive therapy to treat AE symptoms	1.2 (0.5-2.7) p=0.74	1.1 (0.4-2.8) p=0.61	0.8 (0.1-6.0) p=0.67
Regimen changed	0.5 (0.2-1.8) p=0.31	0.5 (0.1-2.6) p=0.37	0.6 (0.1-4.3) p=0.50
Adverse events lasting≥3 months	3.1 (1.4-7.2) p=0.002	3.6 (1.03-12.5) p=0.009	1.9 (0.5-7.2) p=0.33

Numbers represent risk ratio (RR) point estimates, their corresponding 95% confidence intervals in brackets, and p-values; HIV= human immunodeficiency virus; AEs= adverse events

There were HIV stratum-specific differences in the connection between occurrence of moderate-to-severe adverse events and those that lasted for three or more months. The risk ratios were RR=3.6 (95% CI 1.03-12.5, p=0.009) for the HIV infected sub-group versus RR=1.9 (95% CI 0.5-7.2, p=0.33) for the HIV uninfected one, demonstrating effect modification by HIV infection status (Table 4).

On the contrary, the occurrence of moderate-to-severe adverse events was not a determinant of the clinician's decision to prescribe adjunctive medicines for certain adverse events (RR=1.2, 95% CI 0.5-2.7, p=0.74) or to change the entire DR-TB treatment regimen (RR=0.5, 95% CI 0.2-1.8, p=0.31) as shown in Table 4.

DISCUSSION

We found a high occurrence (89%) of any adverse event during DR-TB treatment. Similar findings have been reported elsewhere in the study by Koju *et al.* in Nepal who found that 80% of patients experienced at least one adverse event during treatment of tuberculosis. [10] Likewise, Leimane and co-researchers reported that 86% of patients in their study in Latvia experienced an adverse event, [11] while Bloss *et al.* reported an adverse event frequency of 79% in the same country. [12] Also, Shin *et al.*, have reported that 73% of MDR-TB patients in their Russian cohort experienced at least one adverse event. [13] This clearly shows that second-line anti-TB medicines are associated with a high frequency of adverse events.

The cumulative incidence of moderate-to-severe adverse events in our cohort was 46 events in 100 DR-TB patients. This finding is similar to that of Lanternier *et al.*, who reported an incidence of severe adverse events of 45.2 ±11.3 per 100 person-years.

Chapter 2.3

[14] Such a high incidence of moderate-to-severe adverse events is a cause for concern for DR-TB programme managers, patients and clinicians.

In the present study, HIV co-infected DR-TB patients experienced more moderate-to-severe adverse events compared with the HIV uninfected patients (58 versus 20 events, p=0.02). The HIV co-infected patients had a four-fold risk of experiencing moderate-to-severe adverse events compared with the HIV uninfected patients (HR = 4.0; 95% CI 1.5 – 10.5, p=0.006). Similar findings have been reported by other researchers. For example, in Lima, Peru, Chung-Delgado *et al.* found that HIV infection increased the risk of adverse events during TB therapy by 3.45 (95% CI 1.61-7.45). [5] Similarly, Lanternier *et al.* found that HIV infection increased the risk of TB treatment-associated adverse events by 3.9 (95% CI 2.1-7.5). [14] Therefore, we urge clinicians to be more vigilant and to look out for potential moderate-to-severe adverse events when treating HIV co-infected DR-TB patients. This will help them to identify adverse events early enough so that appropriate measures could be taken to mitigate them.

None of the second-line anti-TB or antiretroviral medicines was statistically significantly associated with the occurrence of moderate-to-severe adverse events. This was rather surprising as second-line anti-TB medicines are known to elicit moderate-to-severe adverse events. [13,15] We argue that the failure to detect any statistically significant associations may have arisen from the low power of the study, rather than from a real biological difference in the way the medicines acted in the patients included in our study. However, amikacin, ciprofloxacin and ethambutol seemed to have a much higher risk than the other second-line anti-TB medicines. These three medicines tended to be prescribed together as part of a DR-TB regimen. This observation needs to be further investigated in a more powered and appropriately designed study that is capable of ruling out bias and confounding, for example, confounding by co-medication and confounding by indication of the medicines used for the treatment of DR-TB infection and concomitant HIV infection.

The frequency of a clinician reducing the dose or stopping the suspected offending medicine was 29%, while that of completely changing the treatment regimen was 18%. These findings are comparable with those of Prasad *et al.* where 21% of the patients developed major adverse events that required stoppage or change of the offending medicines. [16] Similarly, Bloss *et al.* have reported dosage reduction in 20% of the patients treated for MDR-TB. [12] On the other hand, Torun *et al.* reported a higher rate (55%) of withdrawal or discontinuation of second-line medicines during MDR-TB treatment. [15] As such, we advocate for clinicians to always consider reducing the dose, discontinuing or substituting the suspected offending medicine when managing moderate-to-severe adverse events during the treatment of DR-TB.

Moderate-to-severe adverse events were the main reason for clinicians' decision to either reduce the dose or to stop a specific DR-TB medicine (RR=3.8, 95% CI 1.2-11.8,

p=0.01). This remained true, irrespective of the patients' HIV infection status. However, patients co-infected with HIV tended to suffer more from adverse events that lasted for three or more months (RR=3.6, *p*=0.009) compared with the HIV uninfected patients (RR=1.9, *p*=0.33). The reason for the longer duration of some adverse events in HIV co-infected patients is unclear, but we think that it could be related to the patients' weakened immune status and to the pharmacological interactions between some of the anti-TB and antiretroviral medicines. [2, 3] Clinicians need to be alert that moderate-to-severe adverse events in patients on concomitant DR-TB and HIV treatment may potentially last for at least three months. Such persistence of moderate-to-severe adverse events could negatively impact the patients' ability to adhere to both treatments, possibly compromising patients' DR-TB and HIV treatment outcomes.

Study limitations and strengths

The adverse events described in our study were symptomatic and were clinician or patient-reported. The over- or under-reporting of some of the adverse events, especially those that require objective confirmatory tests, may have biased the data. Furthermore, since no causality assessments were done, it was not always possible to attribute particular adverse events to a specific medicine at the individual patient level. Despite this limitation, we were able to reveal the magnitude and nature of the association between moderate-to-severe adverse events and HIV co-infection. We were also able to elucidate on the relationship between the occurrence of moderate-to-severe adverse events and the various medical interventions made to manage the adverse events as well as the outcomes of these adverse events. By unravelling some of the complexities of DR-TB treatment, this study contributes to the epidemiology of adverse events in DR-TB treatment, hence enriching the evidence base upon which clinicians and TB programme managers may use to make decisions on improving treatment of DR-TB infection.

CONCLUSIONS

Moderate-to-severe adverse events are common during DR-TB treatment. They are more likely to occur and to persist in HIV co-infected patients than in HIV uninfected ones. Clinicians may alleviate the discomfort and reduce the harm of such adverse events by reducing the dose, stopping or by changing the suspected offending medicine. Managers of TB control programs should strengthen pharmacovigilance systems so that clinically important adverse events could be detected early and control or mitigation measures instituted in time, for example, through revision of treatment guidelines. We recommend a larger study to generate more precise and conclusive findings on the

determinants of the moderate-to-severe adverse events and the effect of the events on DR-TB treatment outcomes and patients' health-related quality of life.

ACKNOWLEDGEMENT

REFERENCES

1. Ministry of Health and Social Services (MoHSS). National Tuberculosis and Leprosy Programme: Second Medium Term Strategic Plan for Tuberculosis and Leprosy, 2010-2015. Windhoek: MoHSS; 2010.

2. Ministry of Health and Social Services (MoHSS). Report on the 2008 National HIV Sentinel Survey. Windhoek: MoHSS; 2008.

3. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 2nd ed. Windhoek: MoHSS; 2006.

4. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc lung Dis. 2004 Nov;8(11):1382–4.

5. Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The Treatment of Multidrug-Resistant Tuberculosis in Turkey. N Engl J Med. Massachusetts Medical Society ; 2001 Jul 19;345(3):170–4.

6. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet. 2005;365(9456):318–26.

7. Törün T, Güngör G, Ozmen I, Bölükbaşi Y, Maden E, Biçakçi B, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc lung Dis. 2005 Dec;9(12):1373–7.

8. Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rüsch-Gerdes S, et al. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLoS One. 2007 Jan;2(11):e1126.

9. Nahar BL, Hossain AM, Islam MM, Saha DR. A comparative study on the adverse effects of two anti-tuberculosis drugs regimen in initial two-month treatment period. Bangladesh J Pharmacol. 2008 Jan 7;1(2):51–7.

10. Papastavros T, Dolovich LR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ. 2002 Jul 23;167(2):131–6.

11. Furin JJ, Mitnick CD, Shin SS, Bayona J, Becerra MC, Singler JM, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc lung Dis. 2001 Jul;5(7):648–55.

12. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc lung Dis. 2007 Dec;11(12):1314–20.

13. Lanternier F, Dalban C, Perez L, Bricaire F, Costagliola D, Caumes E. Tolerability of anti-tuberculosis treatment and HIV serostatus. Int J Tuberc lung Dis. 2007 Nov;11(11):1203–9.

14. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. Int J Tuberc lung Dis. 2010 Mar;14(3):275–81.

15. Tupasi TE, Gupta R, Quelapio MID, Orillaza RB, Mira NR, Mangubat N V, et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006 Sep;3(9):e352.

Chapter 2.3

16. Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer PE, Satti H. Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. PLoS One. 2009 Jan;4(9):e7186.

17. World Health Organization (WHO). Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010.

18. Cain KP, Kanara N, Laserson KF, Vannarith C, Sameourn K, Samnang K, et al. The epidemiology of HIV-associated tuberculosis in rural Cambodia. Int J Tuberc lung Dis. 2007 Sep;11(9):1008–13.

19. Jager P De, Altena R Van. Hearing loss and nephrotoxicity in long-term aminoglycoside. Int J Tuberc Lung Dis. 2002;6(April):622–7.

20. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5.

21. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. Antimicrob Agents Chemother. 1989 Jun;33(6):797–800.

22. Nadol J. Hearing loss. N Engl J Med. 1993;329(15):1092–102.

23. Tan KH-V, Mulheran M, Knox AJ, Smyth AR. Aminoglycoside Prescribing and Surveillance in Cystic Fibrosis. Am J Respir Crit Care Med. American Thoracic Society; 2003 Mar 15;167(6):819–23.

24. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007 Jan;13(1):119–26.

Chapter 2.4

Adverse Events and Patients' Perceived Health-Related Quality of Life at the End of Multidrug-Resistant Tuberculosis Treatment in Namibia

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ABSTRACT

Objectives: The health-related quality of life (HRQoL) of patients completing multidrug-resistant tuberculosis (MDR-TB) treatment in Namibia and whether the occurrence of adverse events influenced patients' rating of their HRQoL was evaluated.

Methods: A cross-sectional analytic survey of patients completing or who recently completed MDR-TB treatment was conducted. The patients rated their HRQoL using the simplified Short Form-™ (SF-8) questionnaire consisting of eight Likert-type questions. Three supplemental questions on the adverse events that the patients may have experienced during their MDR-TB treatment were also included. Scoring of HRQoL ratings was norm-based (mean =50, standard deviation =10) ranging from 20 (worst health) to 80 (best health), rather than the conventional 0-100 scores. We evaluated the internal consistency of the scale items using the Cronbach's alpha, performed descriptive analyses, and analyzed the association between the patients' HRQoL scores and adverse events.

Results: Overall, 36 patients (20 males, 56%) aged 17-54 years (median =40 years) responded to the questionnaire. The median (range) HRQoL score for the physical component summary was 58.6 (35.3-60.5), while the median score for the mental component summary was 59.3 (26.6-61.9), indicating not-so-high self-rating of health. There was good internal consistency of the scale scores, with a Cronbach's alpha value of >0.80. In all, 32 (89%) of the 36 patients experienced at least one adverse drug event of any severity during their treatment (median events =3, range 1-6), of which none was life-threatening. The occurrence of adverse events was not related to HRQoL scores. For patients reporting zero to two events, the median (range) HRQoL score was 56.8 (44.4-56.8), while for those reporting three or more events, the median score was 55.2 (38.6-56.8); P=0.34 for difference between these scores.

Conclusions: Patients completing treatment for MDR-TB in Namibia tended to score moderately low on their HRQoL, using the generic SF-8 questionnaire. The occurrence of adverse events did not lead to lower HRQoL scores upon treatment completion.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) has become a major public health problem, especially in developing countries, where the MDR-TB burden is the highest. [1] Unlike the treatment of drug-sensitive Mycobacterium tuberculosis, the treatment of MDR-TB takes a long time, is complex and is frequently associated with the occurrence of various adverse drug reactions. [2–8] Some of these adverse drug reactions, such as ototoxicity, nephrotoxicity, and hepatotoxicity, could severely diminish a person's health-related quality of life (HRQoL). [9–12] Besides, the success rates of global MDR-TB treatment have been generally poor, at ~48%, due to several factors that included the patients' difficulties with adhering to prescribed MDR-TB treatment regimens. [13,14] The occurrence of severe or serious treatment-related adverse events, along with other disease-related sequelae, may impair patients' ability to perform activities of daily life during or after MDR-TB treatment. [12] This calls for the routine assessment of the HRQoL of patients undergoing MDR-TB treatment. [12]

Over the past decade, there has been an increasing interest on the impact of tuberculosis (TB) treatment on patient's HRQoL. [12,15] However, most of the research published on this topic has primarily focused on drug-sensitive TB. For example, out of the 27 studies reviewed by Brown *et al.*, [12] only one study pertained to MDR-TB. Similarly, in the systematic review by Guo *et al.*,15 only one study included patients diagnosed with drug-resistant TB. Notably, none of these studies analyzed the relationship between patients' HRQoL and the occurrence of adverse events in the context of MDR-TB treatment.

Several instruments for measuring patients' HRQoL have been used in previous studies. [12,15] The instruments include the Short Form-36 (SF-36) questionnaire, the World Health Organization Quality of Life-BREF tool (WHOQOL-BREF), the EuroQol five dimensions questionnaire (EQ-5D), the EuroQol visual analogue scale (EQ-VAS), the Dhingra and Rajpal-12 questionnaire (DR-12), the Functional Assessment of Chronic Illness Therapy-TB questionnaire (FACIT-TB), the Liebowitz Social Anxiety Scale, and the Airway Questionnaire 20. All these instruments except the EQ-5D and the EQ-VAS are fairly long and require substantial effort by the respondent to complete.

We searched for short versions of the generic HRQoL questionnaires and identified the SF-8™ (SF-8) questionnaire, developed by QualityMetric. The SF-8 questionnaire is the shortest of the short form family of HRQoL questionnaires and has one question for each of the eight concepts (health dimensions) that are measured by the longer version of SF-36 questionnaire. [16] This questionnaire has been tested for reliability and validated in two large settings in Uganda [17] and in Japan (among teachers after enforcement of a smoke-free school policy). [18]

To date, no published study has evaluated the association between the reporting of adverse events and patients' HRQoL scores at the end of MDR-TB treatment. Our study objective, therefore, was to investigate the impact of adverse events on perceived HRQoL in patients at the end of MDR-TB treatment in Namibia using the SF-8 questionnaire.

METHODS

Study design and patient selection

This was a cross-sectional analytic survey conducted among a consecutive sample of patients treated for MDR-TB in Namibia. The patients were considered eligible for the study if they were treated for MDR-TB using second-line drugs, were at the age of 16 years or older, were in their final month of treatment or had completed their treatment within the past 3 months, were reachable, and were willing to participate in the study. Those who defaulted or did not complete treatment were not considered for the study. Participants were recruited as outpatients using the MDR-TB register maintained at the main clinic where they received their treatment. For persons who had finished their treatment within the past 3 months, the nurse at the clinic called their phone numbers, inviting them to participate in the survey. Since there were few eligible patients, each patient was approached to participate in the study. The target sample size was 138 patients. This was determined based on the following assumptions: anticipated minimum score differences of 0.5 to consider change when assessing differences between a group mean and a fixed norm, an alpha score of 0.05, two-tailed t-test, and a statistical power of 80%. [19]

Setting and MDR-TB treatment

The study was conducted within the public sector health service of Namibia. Once diagnosed with MDR-TB infection, the patients were admitted to the MDR-TB treatment ward nearest to them where they were initiated on the intensive phase of treatment that included a course of kanamycin injections and at least four other oral second-line anti-TB drugs for at least 6 months until the patient converted to sputum smear and culture negative. The oral anti-TB drugs used were cycloserine, ethionamide, levofloxacin, pyrazinamide, and sometimes ethambutol. This drug regimen was in accordance with Namibia's clinical guidelines for the treatment of MDR-TB that were current at the time of the study. [20] After the intensive phase, the patients were discharged on oral anti-TB drugs and referred to the outpatient clinic closest to them for their continuation phase of treatment. This treatment phase often lasted for at least 12 months depending on how long it took the patient to be cured of the infection. [20] The continuation phase treatment was administered daily on an outpatient basis at a hospital, health

center, or clinic nearest to the patient and was supervised by a nurse. A medical doctor periodically reviewed the patients for their progress on treatment. The patients were prompted to report to the medical doctor or nurse any adverse events or concerns they had regarding their medication, throughout the course of their treatment. As part of routine care, doctors and nurses read to the patients a list of 18 adverse events commonly encountered with second-line anti-TB drugs, to trigger the patients' recollection. The adverse events reported by the patients were documented in the patients' medical records, as previously described elsewhere. [21,22] If a patient failed to appear at the outpatient clinic for their medication appointment, the patient was immediately traced by a community health care worker so that treatment is not interrupted.

Questionnaire

The SF-8 questionnaire is a simple tool consisting of eight questions about a person's self-assessment of his or her HRQoL at a particular point in time. [16] Four questions of the SF-8 questionnaire address the physical component of health, while the other four questions address the mental health component. The physical health dimensions are physical functioning (PF), role physical (RP), general health (GH), and bodily pain (BP). The mental health dimensions are vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Each question has five or six Likert-type responses. We also included three supplemental questions on the occurrence of adverse events during MDR-TB treatment and on the age and sex of the study participants (Figure S1).

Data collection

The nurses at the MDR-TB treatment clinics were informed about the study and were trained to use the SF-8 questionnaire. Consenting patients were invited to respond to the survey that was administered by the trained nurses. The patients were asked to rate their health for each of the eight items of the SF-8 questionnaire. The patients also reported the adverse events that they recalled having experienced during their treatment. This was further supplemented by the information on adverse events that was recorded on the patients' treatment card. The survey was consecutively conducted for each consenting participant from January 1, 2015 to April 30, 2015.

Data analysis

The patients' responses were entered into the SF-8 QualityMetric Health Outcomes™ Scoring Software 4.5, which was supplied by the proprietor of the SF-8 questionnaire – QualityMetric, Optuminsight Life Sciences. [16] The software automatically computes individual patient scores based on their self-ratings of each item on the questionnaire, using a norm-based scoring method. [23] In a norm-based scoring approach, each scale is scored to have a standardized mean and standard deviation (SD), relative to

the general population scores. [24] For the SF-8 questionnaire, the scale item values are normed by the scoring tool so that 50 is equal to the mean of the norm sample and 10 is equal to the SD of the norm sample. [23] The norm sample has been selected by the developers of the questionnaire based on the US general population. [25] Scores above or below 50 were considered above or below the general average, respectively. The physical component summary (PCS) and the mental component summary (MCS) scores were also computed by the tool. Higher PCS and MCS scores indicate better health. A two-sided Wilcoxon signed-rank test, with an alpha of 0.05, was used to determine whether the difference in the median PCS and MCS scores was statistically significant. Furthermore, the HRQoL scores for each of the eight items were then exported to SPSS version 12.0.1 and R for further analysis and for calculating the Cronbach's alpha for the physical component and the mental component scale items, respectively. The Cronbach's alpha is a measure of the internal consistency (reliability) of a psychometric scale. Generally, a Cronbach's alpha of ≥0.70 is considered to indicate satisfactory reliability of a scale. [26] In addition, we used 2×2 contingency tables to perform the Fisher's exact test (rather than the chi-square test) due to the small cell values and to compute P-values of the association between the proportion of patients who experienced three or more adverse events and those who rated their HRQoL scores <50 points. The level of statistical significance was 0.05.

Ethical statement

Participation in this study was voluntary. Nurses at the participating MDR-TB treatment sites explained the study aim and objectives to eligible patients and sought their written informed consent. Only consenting patients were invited to respond to the questionnaire. All participants provided written informed consent. In the event that a patient declined to participate in the study, the patient's decision did not compromise the care that the patient received from the clinic. Furthermore, the patients could stop responding to the questionnaire at any time, without reprisals. The data were analyzed anonymously, and the results were reported in an aggregate manner, for patient confidentiality. The study was approved by the institutional review board of Utrecht University (reference: UP1307) and the research and ethics committee of the Namibian Ministry of Health and Social Services (reference: 17/3/3, dated on December 19, 2013).

RESULTS

A total of 36 patients responded to the SF-8 questionnaire as well as the supplementary questions. Of these respondents, 20 (56%) were males, and the median age of the patients was 40 years, ranging from 17 to 54 years.

The HRQoL scores of individual patients for each of the eight SF-8 dimensions ranged between 25 and 65 points (Figure 1). There was considerable interpersonal variation in the patients' scores. Patient scores were highest for BP, GH, and VT. However, the PF, RP, and the RE dimensions tended to be rated poorly by the patients, with each of these dimensions achieving mean ratings of 52.4, 52.1, and 51.0, respectively. For the entire group, the median (range) HRQoL score for the PCS was 58.6 (35.3–60.5), while it was 59.3 (26.6–61.9) for the MCS. The difference in the median PCS and MCS scores was small (0.68), but was statistically significant (P=0.005).
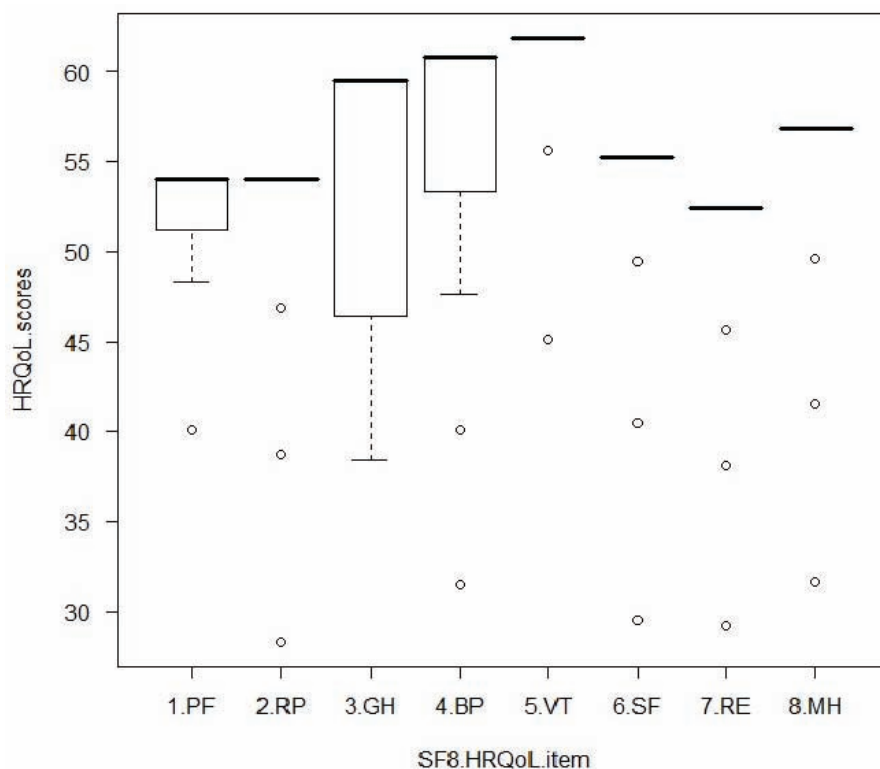
Figure 1: Boxplots comparing the variation in health-related quality of life scores for each SF8™ item
Legend: Physical component: PF=Physical Functioning; RP=Role Physical; GH=General Health; BP=Bodily Pain; Mental component: VT=Vitality; SF=Social Functioning; RE=Role Emotional; MH=Mental Health

There was good internal consistency of the scale scores, with a Cronbach's alpha of 0.83 and 0.94 for the PCS and MCS, respectively. Furthermore, as shown in Figure 2, there was essentially no correlation between the PCS and MCS scores (R2=0.24). However, the MCS scores were more variable than the PCS scores. The variance for the MCS was 51.7, while it was 33.8 for the PCS.
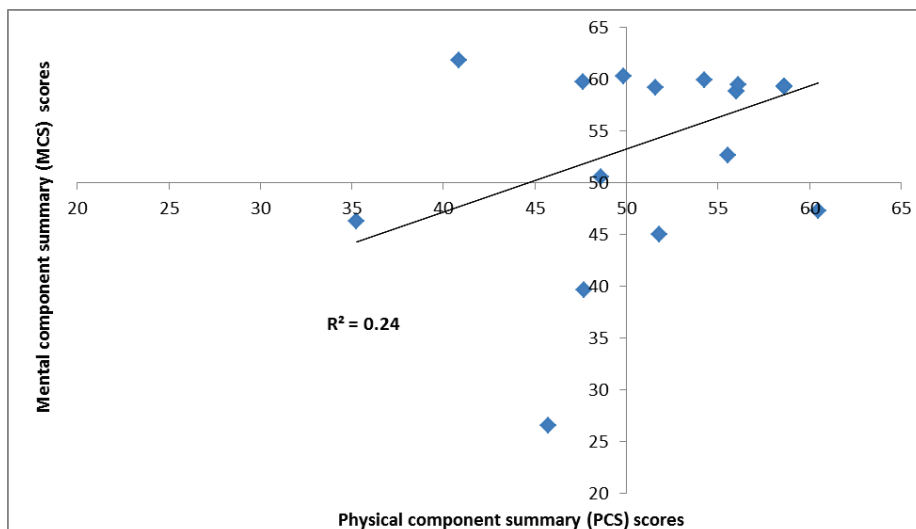
Figure 2: Correlation of the physical and mental component scores

A total of 32 (89%) of the 36 patients in this study reported experiencing at least one adverse drug event of any severity during their treatment (median events =3, range 1–6). The frequency of the reported adverse events is shown in Table 1. None of the adverse events were life-threatening. Except for hearing loss, the other adverse events were not permanent and they subsided when the treatment ended. In addition to these adverse events, the patients complained of painful injections during the intensive phase of treatment, taking too many tablets, having to undergo lengthy daily treatment schedules and some tablets tasting awful. Some of the patients lamented that the entire treatment experience was very stressful for them. Despite these medication-related challenges, all the patients completed their treatment and were cured of the MDR-TB infection after 20–24 months of taking anti-TB medicines on a daily basis.

Only four of the 32 patients (12.5%) who experienced at least one adverse event rated their HRQoL <50 points. The HRQoL scores for these four patients were 38.6, 42.0, 48.4, and 49.9. Figure 3 shows the association between the total number of adverse events reported per patient and their overall HRQoL score. No association was found between the occurrence of adverse events and patients' ratings of their HRQoL (P=0.34) at the end of MDR-TB treatment. Neither did the occurrence of ototoxicity (P=0.45), gastrointestinal adverse events (P=0.70), joint pain, or neuropathy (P=0.30) significantly influence the patients' HRQoL scores (Table 2).

Table 1: Frequency of patients' self-reported adverse events

Adverse event	Patients reporting (N=36)
Hearing loss	9 (25%)
Vomiting	8 (22%)
Joint pain	8 (22%)
Nausea	7 (19%)
Tinnitus	6 (17%)
Dizziness	6 (17%)
Abdominal pain	6 (17%)
Headache	5 (14%)
Fatigue	5 (14%)
Vision problems	4 (11%)

Chapter 2.4
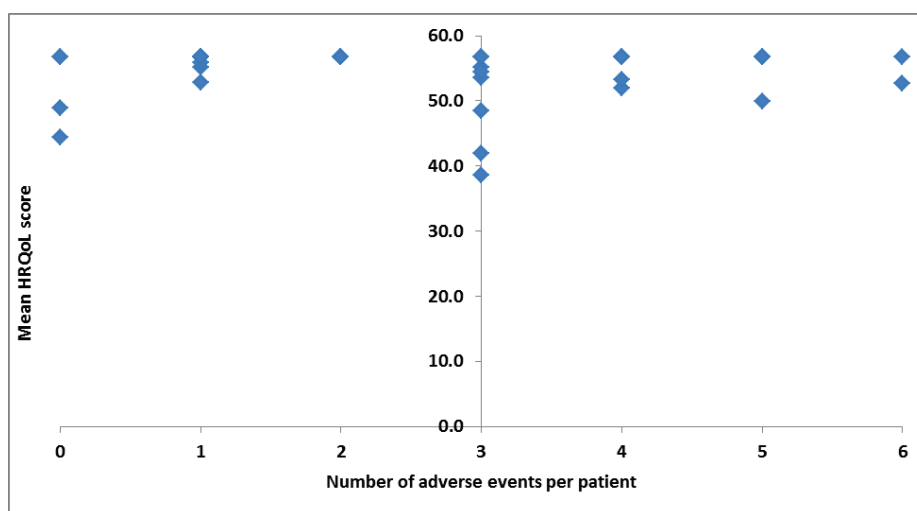
Figure 3: Patients' mean Health Related Quality of Life (HRQoL) scores by number of adverse events experienced by patients

Table 2: Occurrence of adverse events and patients' rating of their health-related quality of life

Type of adverse event	Categories	Proportion of patients with HRQoL scores < 50	*p*-value (Fisher exact test)
Any adverse event	0-2 events	3/17 (18%)	0.45
	≥ 3 events	6/19 (32%)	
Ototoxicity	Absent	6/20 (30%)	0.70
(hearing loss and tinnitus)	Present	3/16 (19%)	
Gastrointestinal events*	Absent	6/22 (27%)	1.00
	Present	3/14 (21%)	
Joint pain and neuropathy	Absent	5/25 (20%)	0.41
	Present	4/11 (36%)	

*Includes nausea, vomiting, abdominal pain and diarrhea

DISCUSSION

In our study, patients' HRQoL ratings were moderately low at the end of their MDR-TB treatment. The maximum overall HRQoL score of the patients was 61 points, while the lowest was 25 points, which is way below the ideal HRQoL rating of 80 norm-based points. PF, RP, and RE were the lowest-rated dimensions of health, barely achieving ratings >55 points. No association was found between these HRQoL scores and the occurrence of adverse events.

The majority of the surveyed patients experienced at least one adverse event during their treatment. These adverse events were hardly debilitating or life-threatening. The occurrence of the adverse events was unrelated to the patients' HRQoL scores. This finding might appear surprising and counterintuitive, but it has to be interpreted carefully. First, we have previously reported that almost all the adverse events experienced by the patients during MDR-TB treatment occur within the first 8 months of treatment (also known as the intensive phase of treatment). [3] Very few new adverse events, if any, occur in the continuation phase of treatment. However, some adverse events that originally developed in the intensive phase, such as the permanent adverse events, may persist into the continuation phase of treatment. The continuation phase typically lasts for at least 12 months depending on how long it takes for a patient to be bacteriologically cured. Except for the few persistent or permanent adverse events, most adverse events occurring within the first 8 months of treatment resolve by the time the patient progresses into the continuation phase of treatment. At the time of treatment completion, almost all the adverse events have fully resolved, thereby negligibly impacting on a patient's assessment of his/her HQRoL at the end of treatment.

Second, one would ask whether the occurrence of persistent or permanent adverse events may influence a patient's HRQoL rating at treatment completion. In the current study, hearing loss was the only permanent adverse event that was most frequently

cited by the patients. Yet, the occurrence of hearing loss did not influence the patients' rating of their HRQoL. A potential explanation is that the patients may have already adjusted to their hearing loss by the time they completed their MDR-TB treatment; hence, they did not consider the hearing loss to be a major handicap to worry about. Indeed, the patients may have resigned themselves into accepting these adverse events as part of their MDR-TB treatment knowing that the benefits far outweigh any adverse event, making the patients not to complain about the events. Alternatively, some of the patients may have experienced only mild forms of hearing loss, while others may have received hearing aids that corrected for the hearing deficit, perhaps further explaining why they rated their HRQoL similarly to those who did not experience hearing loss.

Third, we could have surveyed a biased sample of well-motivated and tolerant patients who were determined to go through their entire MDR-TB treatment schedule despite the challenges posed by any adverse event(s) they may have encountered during the course of treatment. Such a group of treatment "survivors" might be the patients who did not suffer from the potentially severe or serious adverse events, which may have lowered their HRQoL rating. This is an inherent limitation of our study design because we did not compare the HQRoL of patients completing MDR-TB treatment with those who might have dropped off from their treatment at an earlier stage.

The small sample size in our study was a major limitation. We were able to survey only 36 of the targeted 138 (26%) respondents. This low sample coverage underpowered the ability of the study to detect the predefined differences if they would exist. However, the current data show that there is no association between the occurrence of adverse events and the patients' HRQoL at the end of MDR-TB treatment.

Last, as postulated by Stewart and Nápoles-Springer [27] and by Lee *et al.*, [28] the patients' perception of their HRQoL may vary according to the patients' socioeconomic background and cultural context. It is, therefore, possible that a patient raised up in a developing country context, such as Namibia, may rate his/her health in the presence of aminoglycoside-induced hearing loss differently from a patient raised up and living in a developed country setting who experiences a similar condition. Such differences in people-perceived HRQoL may depend on the individual's tolerance and acceptance to live with some health conditions, as well as the support availed to the patient through the social structures or the health system in which he or she lives. It would be advisable to confirm this postulation in a larger, multi-country comparative study.

The high Cronbach's alpha values (>0.8) and the lack of correlation between the physical component and mental component scores show good psychometric properties of the SF-8 questionnaire. This compares favorably with the good Cronbach's alpha values of 0.82 for the physical dimension and 0.87 for the mental dimension as reported by Severo *et al.*, [29] who used the Portuguese version of the SF-36 questionnaire. However, it is important to note that some scholars have cautioned against the use of

Chapter 2.4

Cronbach's alpha in assessing the reliability of tools for measuring HRQoL. [30,31] Our findings indicate that the SF-8 questionnaire is a simple, reliable tool that could be used for the routine measurement and clinical monitoring of changes in the HRQoL of patients treated for MDR-TB, especially at an aggregate or group level.

The findings of the current study have important programmatic and clinical implications for the treatment of MDR-TB, particularly in Namibia. Although there was no correlation between the occurrence of treatment-related adverse events and the patients' HRQoL scoring, we encourage TB program managers and clinicians to pay closer attention to changes in HRQoL in the patients undergoing MDR-TB treatment. While we could not demonstrate it, there is a possibility that the HRQoL of the patients in our study may have transiently diminished at the earlier stages of their MDR-TB treatment (in the intensive phase), due to the occurrence of adverse events. Our argument is informed by the various studies of patients treated for drug-susceptible TB, which have shown that the patients' HRQoL ratings change at various stages in the course of their TB treatment. [12,15,32,33]

Among the patients who successfully completed their prescribed MDR-TB treatment, it appears that disease factors, rather than treatment-related adverse events, may have a bigger role in influencing the HRQoL of the patients. [34] Better clinical management of the potentially serious or severe adverse events experienced by the patients will ensure that the adverse events do not significantly contribute to the decrement of patients' HRQoL. We recommend that a larger longitudinal study be conducted to determine the relative role that MDR-TB-disease and its treatment may play in influencing the patients' HRQoL ratings.

Since the SF-8 questionnaire is a reliable, simple, and easy-to-apply tool, we recommend TB program managers and clinicians to routinely use it to monitor changes in HRQoL in the patients. Such routine patient HRQoL measurements could be aggregated at a programmatic level to monitor the groupwise impact of MDR-TB treatment on the patients' HRQoL as a quality of care indicator for the MDR-TB treatment program.

A major strength of the current study is that the questionnaire used was short and easy to administer. However, being cross-sectional, the study only collected data at one point in time (at the end of MDR-TB treatment). Consequently, it was not possible for us to compare the patients' baseline HRQoL scores with their subsequent scores at various points during the treatment and at the end of the treatment. Moreover, there could have been biases caused by the patients' recall and selective self-reporting of adverse events and also by TB clinic nurses administering the questionnaire to the patients because they were the same nurses who provided care to the patients. However, we addressed this challenge by extracting supplemental data on adverse events from the patients' MDR-TB treatment records.

CONCLUSIONS

Patients who completed their MDR-TB treatment in Namibia tended to score moderately low on their HRQoL using the generic SF-8 questionnaire. No association was found between the patients' HRQoL scores upon treatment completion and the occurrence of adverse events. This finding needs to be confirmed in a larger study that measures HRQoL at baseline, at multiple time points during the MDR-TB treatment phases and at the completion of treatment so that the changes in HRQoL may be ascertained.

ACKNOWLEDGEMENT

Chapter 2.4

REFERENCES

1. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland; 2008.

2. Sturdy A, Goodman A, José RJ, Loyse A, O'Donoghue M, Kon OM, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. J Antimicrob Chemother. 2011;66(8):1815–20.

3. Sagwa E, Mantel-Teeuwisse AK, Ruswa N, Musasa JP, Pal S, Dhliwayo P, et al. The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. South Med Rev. 2012;5(1):6–13.

4. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc lung Dis. 2004;8(11):1382–4.

5. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc lung Dis. 2007;11(12):1314–20.

6. Furin JJ, Mitnick CD, Shin SS, Bayona J, Becerra MC, Singler JM, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc lung Dis. 2001;5(7):648–55.

7. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. Int J Tuberc lung Dis. 2010;14(3):275–81.

8. van der Walt M, Lancaster J, Odendaal R, Davis JG, Shean K, Farley J. Serious treatment related adverse drug reactions amongst anti-retroviral naïve MDR-TB patients. PLoS One. 2013;8(4):e58817.

9. Patel P, Ramanuj V, Bala D. Assessment Quality of Life (QoL) of TB patients registered in Tuberculosis units of Ahmedabad Municipal Corporation area by using WHO Short Form -36. Sch J Appl Med Sci. 2014;2(6F):3303–6.

10. Muniyandi M, Rajeswari R, Balasubramanian R, Nirupa C, Gopi PG, Jaggarajamma K, et al. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. Int J Tuberc lung Dis. 2007;11(8):887–92.

11. Sharma R, Yadav R, Sharma M, Saini V, Koushal V. Quality of life of multi drug resistant tuberculosis patients: a study of north India. Acta Med Iran. 2014;52(6):448–53.

12. Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. Int J Infect Dis. 2015;32:68–75.

13. World Health Organization (WHO). Global Tuberculosis Report, 2014. Geneva, Switzerland; 2014.

14. World Health Organization (WHO). MDR-TB 2014 Update. Geneva, Switzerland; 2014.

15. Guo N, Marra F, Marra C a. Measuring health-related quality of life in tuberculosis: a systematic review. Health Qual Life Outcomes. 2009;7:14.

16. OptumInsight Life Sciences Inc. SF-8 Health Survey [Internet]. [cited 2015 Sep 5]. Available from: https://www.optum.com/optum-outcomes/what-we-do/health-surveys/sf-8-health-survey.html

17. Roberts B, Browne J, Ocaka KF, Oyok T, Sondorp E. The reliability and validity of the SF-8 with a conflict-affected population in northern Uganda. Health Qual Life Outcomes. 2008;6:108.

18. Kiyohara K, Itani Y, Kawamura T, Matsumoto Y, Takahashi Y. Changes in the SF-8 scores among healthy non-smoking school teachers after the enforcement of a smoke-free school policy: a comparison by passive smoke status. Health Qual Life Outcomes. 2010;8:44.

19. Prieto L, Alonso J, Antó JM. Estimating sample sizes for studies using the SF-36 health survey. J Epidemiol Community Health. BMJ Group; 1996;50(4):473–4.

20. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 3rd ed. Windhoek: MoHSS; 2012.

21. Sagwa E, Ruswa N, Musasa JP, Mantel-Teeuwisse AK. Adverse events during treatment of drug-resistant tuberculosis: a comparison between patients with or without human immunodeficiency virus co-infection. Drug Saf. 2013;36(11):1087–96.

22. Sagwa EL, Mantel-Teeuwisse AK, Ruswa NC. Occurrence and clinical management of moderate-to-severe adverse events during drug-resistant tuberculosis treatment: a retrospective cohort study. J Pharm policy Pract. 2014;7(1):14.

23. Ware JE. Advantages of norm-based scoring of SF health survey. User's Manual for the SF-36v2 Health Survey. 2nd ed. QualityMetric; 2007. p. 81–4.

24. Supina AL, Feeny DH, Carroll LJ, Johnson JA, Lydick E, Epstein R, et al. Misinterpretation with norm-based scoring of health status in adults with type 1 diabetes. Health Qual Life Outcomes. BioMed Central; 2006;4(1):15.

25. Ware JE. How to score and interpret single-item health status measures: a manual for users of the of the SF-8 health survey. Lincoln RI ;Boston MA: QualityMetric, Inc.; 2001. 220 p.

26. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ. IJME; 2011;2:53–5.

27. Stewart AL, Nápoles-Springer A. Health-related quality-of-life assessments in diverse population groups in the United States. Med Care. 2000;38(9 Suppl):II102-24.

28. Lee JE, Fos PJ, Zuniga MA, Kastl PR, Sung JH. Health-related quality of life of cataract patients: cross-cultural comparisons of utility and psychometric measures. Ophthalmic Epidemiol. 2003;10(3):177–91.

29. Severo M, Santos AC, Lopes C, Barros H. Reliability and validity in measuring physical and mental health construct of the Portuguese version of MOS SF-36. Acta meédica Port. 2006;19(4):281–7.

30. Streiner DL. Being inconsistent about consistency: when coefficient alpha does and doesn't matter. J Pers Assess. 2003;80(3):217–22.

31. Konerding U. What does Cronbach's alpha tell us about the EQ-5D? A methodological commentary to "Psychometric properties of the EuroQol Five-Dimensional Questionnaire (EQ-5D-3L) in caregivers of autistic children." Qual Life Res. Springer Netherlands; 2013;22(10):2939–40.

32. Atif M, Syed Sulaiman SA, Shafie AA, Asif M, Sarfraz MK, Low HC, et al. Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study. Health Qual Life Outcomes. 2014;12(1):1–11.

33. Louw J, Peltzer K, Naidoo P, Matseke G, Mchunu G, Tutshana B. Quality of life among tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health care patients in three districts in South Africa. Health Qual Life Outcomes. BioMed Central; 2012;10(1):77.

34. Harries AD, Ade S, Burney P, Hoa NB, Schluger NW, Castro JL. Successfully treated but not fit for purpose: paying attention to chronic lung impairment after TB treatment. Int J Infect Dis. International Union Against Tuberculosis and Lung Disease; 2016;20(8):1010–3.

Chapter 2.4

ADDITIONAL FILE1: SURVEY QUESTIONNAIRE

PART A: SF-8™ questionnaire (http://www.sf-36.org/demos/SF-8.html)

PART B: Questions about medication side-effects during multidrug-resistant tuberculosis treatment

1. When did you start your treatment for drug-resistant tuberculosis?

    Month: _____   *Year: _____*

2. Did you experience any major unpleasant side-effect/s during the course of your tuberculosis treatment that made you feel bad about taking your medications?

    Yes: ▢ (complete table below)   *No: ▢ (go to question 3)*

List below all unpleasant side-effect/s that you remember experiencing	State the month and year when the side-effect/s occurred	Approximately how long did the side-effect/s last (Days/Weeks/ Months)	What did you do to avoid or minimize the side-effect/s?	Have you completely recovered from the side-effect/s	Any comments about your experience taking MDR-TB medicines
a	Month/ Year	____days/weeks/months		Yes / No	
b	Month/ Year	____days/weeks/months		Yes / No	
c	Month/ Year	____days/weeks/months		Yes / No	
d	Month/ Year	____days/weeks/months		Yes / No	
e	Month/ Year	____days/weeks/months		Yes / No	

3. During the **last month of your prescribed TB treatment**, how would you describe the taking of your medication?

Missed taking on more than 5 occasions	*Missed taking on 3-5 occasions*	*Missed taking on 1-2 occasions*	*Never missed taking my medicine*	*Can't remember*

CHAPTER 3

Comparative otologic and renal safety of aminoglycosides and capreomycin in multidrug-resistant tuberculosis treatment

Chapter 3.1

Differences in aminoglycoside and capreomycin ototoxicity based on the World Health Organization VigiBase®

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Inês Ribeiro
Hubert G.M. Leufkens
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ABSTRACT

Purpose: To evaluate the association between the use of streptomycin, amikacin, kanamycin and capreomycin in tuberculosis (TB) treatment and the pharmacovigilance reporting of ototoxicity (deafness or hearing loss, tinnitus and vertigo). Second, to analyze patient demographic and geographic factors that influence the reporting of ototoxicity in TB treatment.

Methods: A case/non-case disproportionality analysis of the VigiBase® individual case safety reports (ICSRs) of patients treated for TB using multidrug regimens that contain either of streptomycin, amikacin, kanamycin or capreomycin. Cases were reports of ototoxicity; non-cases were other adverse drug reactions (ADRs). The unit of analysis was the drug-ADR pair. We calculated reporting odds ratios (RORs) and their 95% confidence intervals (CI). The referent drug was streptomycin.

Results: By June 2014, there were 3361 drug-ADR pairs in VigiBase® (1693 ICSRs) where the parenteral administration of the four drugs for TB treatment was suspected of causing the reported ADRs. Deafness, tinnitus and vertigo were reported in 576 drug-ADR pairs (cases), the rest being other ADRs (non-cases). Reporting of deafness was most disproportionately associated with amikacin use (ROR 9.3; 95%CI 3.8-23.0), followed by kanamycin use (ROR 4.3; 95%CI 1.3-14.2). Reporting of vertigo was inversely associated with capreomycin use (ROR 0.1; 95%CI 0.01-0.4). Geographic region affected the reporting of ototoxicity while age and sex did not.

Conclusion: Spontaneous reporting of deafness cases within VigiBase® was most disproportionately associated with amikacin use, followed by kanamycin. There were regional variations in the global reporting of ototoxicity. These findings should be verified through a follow up study

INTRODUCTION

Ototoxicity (deafness or hearing loss, tinnitus and vertigo) is an important public health problem that is associated with substantial disability, economic and societal costs. [1–3] It can be caused by several factors, including the use of medications like aminoglycosides (e.g. amikacin, kanamycin and streptomycin) or glycopeptides (e.g. capreomycin), which are currently the cornerstone of multidrug-resistant tuberculosis (MDR-TB) treatment, worldwide. [4,5] The prolonged use of aminoglycosides or capreomycin for MDR-TB treatment augments patients' risk of ototoxicity, making the patients prone to this preventable adverse effect if risk mitigation measures are not put in place. [6,7]

The literature on the occurrence and on the comparative risk of the ototoxicity of aminoglycosides and capreomycin in MDR-TB treatment is limited. Previous studies on this subject have focused on the use of various aminoglycosides and capreomycin in experimental animals; on their use for none-TB indications; or have compared the safety of two or three of these drugs but not all the four drugs simultaneously; or sometimes the studies have included other aminoglycosides that are not indicated for tuberculosis treatment. [7,8] Besides, the review by Frymark and colleagues reveals that most of the safety and efficacy studies on these drugs were conducted in the period between the 1970s and 1990s when the prevalence of MDR-TB globally was still low. [7] The global TB epidemiologic circumstances have since changed, and larger numbers of patients diagnosed with MDR-TB are now being treated with amikacin, kanamycin and capreomycin than before, especially in the developing countries. [9,10] The widespread use of aminoglycosides in MDR-TB has made both clinicians and researchers alike to revisit the question of the comparative otological safety of these drugs in real-life clinical use.

There is currently a wealth of untapped information that has accumulated over time in pharmacovigilance databases on the safety of drug use in real life clinical practice that could help to elucidate on differences in the ototoxicity of these drugs in tuberculosis treatment. An example is the World Health Organization (WHO) global database of individual case safety reports (ICSRs), called VigiBase®, [11] which is a repository of readily available data on reported adverse effects of medicines used in actual clinical practice from around the globe.

This study aimed at evaluating the association between the use of four parenteral drugs (amikacin, kanamycin, streptomycin and capreomycin) and the global pharmacovigilance reporting of ototoxicity (deafness, tinnitus and vertigo) in VigiBase®. At the time of conducting the study, these four drugs were recommended by the WHO for the re-treatment of drug-susceptible TB (streptomycin) or for the treatment of drug-resistant TB (amikacin, kanamycin and capreomycin). [6] Second, we analyzed patient

demographic (age and sex) and geographic factors that influenced the reporting of ototoxicity in TB treatment.

METHODS

Setting

The Uppsala Monitoring Centre (UMC) is the WHO Collaborating Centre for International Drug Monitoring that maintains VigiBase®. [11,12] The UMC collects, stores and routinely analyses pharmacovigilance data on reported suspected adverse drug reactions (ADRs) from all the continents of the world, to identify drug safety signals. At a national level, ADRs are reported by healthcare professionals and in some countries by pharmaceutical companies or patients. An ICSR submitted to the database typically contains anonymous patient demographic characteristics (such as age and sex), the suspected drug(s), concomitant medication, one or more reported ADRs and other relevant clinical information, although detailed clinical information is often lacking in many of the reports. [11] These reports are forwarded electronically by the various collaborating national centers to the UMC for analysis and filing in VigiBase®.

Within VigiBase®, the reported ADRs are coded using the WHO Adverse Drug Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA®). [13,14] Drugs suspected of causing the ADR are classified according to the WHO Drug Dictionary, which is linked to the WHO Anatomical Therapeutic Chemical (ATC) system for classifying medicinal drugs. We used medical product codes of the WHO Drug Dictionary to retrieve the records of the drugs of interest.

Study design

We conducted a case/non-case disproportionality analysis of all ICSRs in VigiBase® between 1968 and June 2014 where streptomycin, amikacin, kanamycin or capreomycin was indicated for TB treatment as part of a multidrug regimen and was the principal drug suspected of causing the reported ADR. We used the therapeutic indications stated on the ICSRs to select the records where the drugs were used for the treatment of TB. These anti-TB drugs were identified in VigiBase® using their respective medical product codes. Only records where the drugs were specified to have been administered parenterally (intramuscular, intravenous, subcutaneous or intradermal) were included in the analysis because these are the main routes by which the drugs are administered in TB treatment. Within this selection of ICSRs, we identified all drug–ototoxicity combinations (cases). Ototoxicity was defined as hearing loss or deafness, tinnitus, vertigo or non-specific ototoxicity, using the relevant MedDRA® high level terms and the associated preferred terms.14 All the other drug and non-ototoxic ADR combinations

were considered as non-cases. Patient or reporter consent was not required because the ICSRs in VigiBase® are anonymous.

Covariates

Covariates were limited to the variables that could be retrieved from the standardized structured fields of VigiBase®. These variables included patients' age, sex and the country reporting the suspected ADR. No information was obtained from the free text fields of VigiBase®.

Data analysis

For a particular ICSR in VigiBase®, a drug could be reported with more than one suspected ADR. Likewise, several suspected drugs could be associated with the same ADR. Thus, the unit of analysis for this study was the drug–ADR combination, rather than the unique ICSR itself.

We used frequency counts, percentages, as well as statistical measures of central tendency and dispersion to summarize the basic patient demographic variables and other characteristics of the drug–ADR combinations.

Categorical variables were compared using the chi-square test. Logistic regression analysis was used to assess the strength of the association between the parenteral use of amikacin, kanamycin or capreomycin inTB treatment and the reporting of ototoxicity and other suspected ADRs. Streptomycin was the referent drug because it is mainly used for re-treatment of drug susceptible *Mycobacterium tuberculosis* and not for the drug-resistant strains. The magnitude of the association was expressed as the reporting odds ratio (ROR), with 95% confidence intervals (CI). The ROR is a measure of disproportionality in pharmacovigilance databases. [15–18]

We also analyzed whether the age, sex and geographic location of the patient was associated with the reporting of ototoxicity. The Statistical Package for the Social Sciences (SPSS) software, version 12.0.1 (IBM SPSS software, New York, USA) was used for data analysis.

RESULTS

By June 2014, out of the total 8 658 133 reports filed in VigiBase®, there were 1693 unique ICSRs with 3361 drug–ADR pairs where streptomycin, amikacin, kanamycin or capreomycin was reported to have been parenterally used for the treatment of *M. tuberculosis* infection (Figure 1). Primarily, these four drugs were used for the treatment of pulmonary tuberculosis, basing on the ICSRs where information on the treatment indications was available.
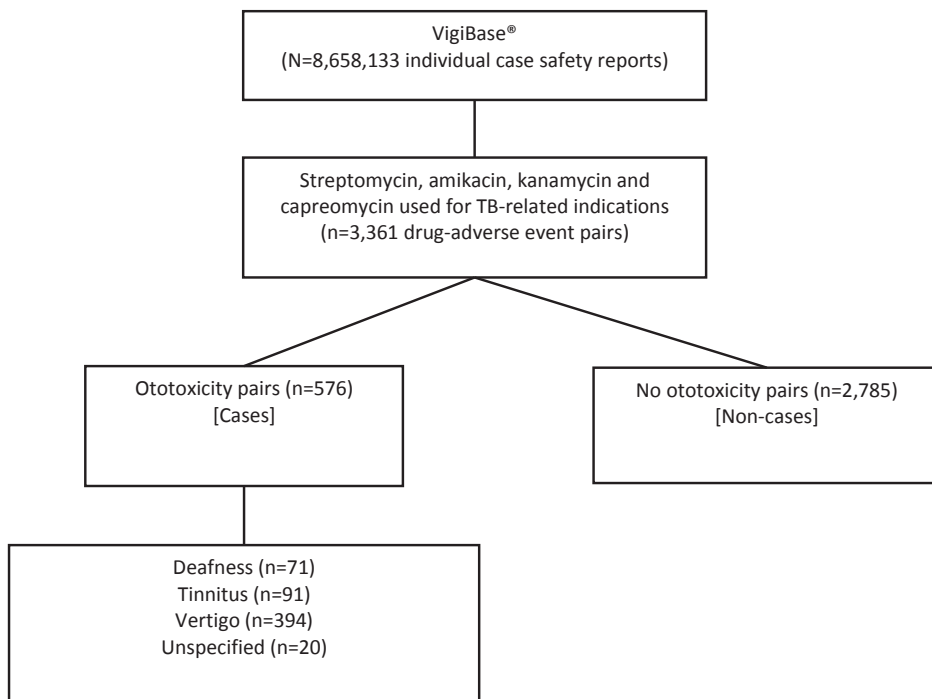
Figure 1: The study flow diagram

Table 1 presents a description of the drug–event pairs that were included in the analysis. Majority (94%) of the patients were treated with streptomycinbased regimens. The reported types of ototoxicity were deafness (n=71), tinnitus (n=91), vertigo (n=394) and non-specific ototoxicity (n=20). The median (interquartile range) patient age was 42 (30–57) years, and males accounted for 1900 (56 %) of the pairs. These reports originated from 56 countries mainly in Asia (n=2034, 60%) and Europe (n=897, 27%).

   In Table 2, we show the specific reported ototoxic adverse reactions (cases) and examples of the nonototoxic adverse reactions (non-cases) that occurred during TB treatment where amikacin, kanamycin, streptomycin or capreomycin was the main suspected drug. It can be seen that the non-ototoxic adverse reactions were diverse in nature, ranging from general, non-specific symptoms such as electrolyte disturbances, pain, fever, malaise and fatigue, to organspecific injury, such as visual impairment, thyroid dysfunction, hepatic failure and renal disorders.

Table 1: Characteristics of the reported suspected drug- adverse reaction pairs

Variable	Categories	Values
Aminoglycoside or capreomycin:	Streptomycin, n (%)	3,164 (94%)
	Kanamycin, n (%)	40 (1%)
	Amikacin, n (%)	40 (1%)
	Capreomycin, n (%)	117 (4%)
Adverse reaction:	Deafness, n (%)	71 (2%)
	Tinnitus, n (%)	91 (3%)
	Vertigo, n (%)	394 (12%)
	Unspecified ototoxicity, n (%)	20 (1%)
	Other adverse reactions, n (%)	2,785 (83%)
Age:	Median (IQR), years	42 (30 – 57)
Sex:	Male, n (%)	1,900 (56%)
	Female, n (%)	1,415 (42%)
	Missing, n (%)	46 (2%)
Region:	Africa, n (%)	164 (5%)
	Americas, n (%)	211 (6%)
	Asia, n (%)	2,034 (60%)
	Europe, n (%)	897 (27%)
	Oceania, n (%)	55 (2%)

n=count; % = percent; IQR=interquartile range

Table 3 shows the crude RORs for the association between the VigiBase® reporting of ototoxicity and the use of amikacin, kanamycin or capreomycin in TB treatment. The reporting of "any ototoxicity" was not disproportionately associated with the use of amikacin or kanamycin, compared to streptomycin use. However, it was associated with a statistically significant lower reporting odds for capreomycin use relative to strepto-mycin use (ROR 0.3; 95%CI 0.1–0.5).

Table 2: Examples of adverse reactions in VigiBase®, suspected to be caused by amikacin, kanamycin, streptomycin or capreomycin use, during tuberculosis treatment

Otototoxic adverse reactions (cases)	Non-otototoxic adverse reactions (non-cases)
1. Hearing impaired (deafness)	14. Dysphagia
2. Tinnitus	15. Eye pain and visual impairment
3. Vertigo	16. Electrolyte disturbances (e.g. hypokalemia)
4. Vestibular disorder	17. Fatigue
	18. Fever
Non-otototoxic adverse reactions (non-cases)	19. Gait disturbance
1. Abdominal pain	20. Gastritis
2. Allergic reaction	21. Hepatic failure
3. Anaphylaxis	22. Hyperthyroidism
4. Ascites	23. Hypothyroidism
5. Cardiac arrest	24. Injection site reaction
6. Cheilitis	25. Malaise
7. Chills	26. Multi-organ failure
8. Conjunctivitis	27. Nausea
9. Constipation	28. Pain
10. Dermatitis and skin rash	29. Pericardial effusion
11. Diarrhea	30. Photophobia
12. Disseminated intravascular coagulation	31. Renal disorders
13. Dyspepsia	32. Vomiting

Table 3: Reporting odds ratios (RORs) for "any ototoxicity" by type of suspected drug

Suspected drug	Total drug-ADR combinations (N=3,361)	Any Ototoxicity (n=576)	Other ADRs (n=2,785)	Crude ROR (95% CI)
Streptomycin	3164	556	2608	Reference
Kanamycin	40	4	36	1.4 (0.7-2.6)
Amikacin	40	10	30	0.7 (0.3-1.7)
Capreomycin	117	6	111	0.3 (0.1-0.5)

ADR=adverse drug reaction; ROR= reporting odds ratio; 95% CI = 95% confidence interval

When assessed by the specific type of ototoxicity as shown in Table 4, the reporting of deafness was disproportionally higher for amikacin use relative to streptomycin use (ROR 9.3; 95%CI 3.8–23.0), followed by kanamycin use (ROR 4.3; 95%CI 1.3–14.2). On the other hand, the reporting of vertigo was inversely associated with the use of capreomycin compared to streptomycin (ROR 0.1; 95%CI 0.01–0.4). However, the reporting of tinnitus in VigiBase® was not significantly disproportionately associated with amikacin, kanamycin or capreomycin use, relative to streptomycin use.

Table 4: Reporting odds ratios (RORs) of specific categories of ototoxicity and the suspected drug

Suspected drug	Deafness (n=71)	Tinnitus (n=91)	Vertigo (n=394)
Streptomycin (n=3,164)	Reference	Reference	Reference
Kanamycin (n=40)	4.3 (1.3-14.2)	0.9 (0.1-6.8)	N/A
Amikacin (n=40)	9.3 (3.8-23.0)	2.9 (0.9-9.7)	0.2 (0.02-1.3)
Capreomycin (n=117)	1.4 (0.4-4.5)	0.6 (0.2-2.6)	0.1 (0.01-0.4)

The numbers in the cell represent the point estimates for the reporting odds ratios (ROR) and their 95% confidence intervals. N/A = not possible to calculate due to some cells containing zero values

Geographical variations in the global reporting of ototoxicity are noticeable in Table 5. Compared to Africa, there was a disproportionately higher reporting of ototoxicity by the Americas (ROR 4.0; 95%CI 1.7–9.3), Asia (ROR 5.1; 95%CI 2.4–11.0) and Europe (ROR 4.8; 95%CI 2.2–10.4). Deafness or tinnitus was the predominant type of ototoxicity reported from the Americas (ROR 5.0; 95%CI 1.4–17.3), while vertigo was mostly reported by countries in Asia (ROR 6.6; 95%CI 2.4–17.9). Europe had almost similar reporting of deafness/tinnitus (ROR 3.8; 95%CI 1.2–12.4) and vertigo (ROR 4.6; 95%CI 1.7–12.6).

Table 5: Geographic variation in the reporting of ototoxicity associated with the use of amikacin, kanamycin, streptomycin or capreomycin during tuberculosis treatment

Region	Any ototoxicity (n=576)	Deafness/Tinnitus (n=162)	Vertigo (n=394)
Africa (n=164)	Reference	Reference	Reference
Americas (n=211)	4.0 (1.7-9.3)	5.0 (1.4-17.3)	2.0 (0.6-6.5)
Asia (n=2,034)	5.1 (2.4-11.0)	2.2 (0.7-7.0)	6.6 (2.4-17.9)
Europe (n=897)	4.8 (2.2-10.4)	3.8 (1.2-12.4)	4.6 (1.7-12.6)
Oceania (n=55)	0.8 (0.2-4.2)	1.0 (0.1-9.7)	0.7 (0.1-6.8)

The numbers in the cell represent the point estimates for the reporting odds ratios (ROR) and their 95% confidence intervals.

Patient age and sex had no influence on the reporting of cases of deafness that were suspected to be caused by the use of aminoglycoside or capreomycin for TB treatment, as shown in Table 6.

Chapter 3.1

Table 6: Influence of patient age and sex on the reporting of deafness suspected to be caused by the use of aminoglycosides or capreomycin in tuberculosis treatment

Variable	Category	Cases (Deafness)	Non-Cases	ROR (95% CI)	P-value
Age (years)	<65	13	503	Reference	
	≥65	57	2,692	1.2 (0.7-2.2)	0.52
Sex	Female	33	1,382	Reference	
	Male	36	1,864	0.8 (0.5-1.3)	0.38

ROR=reporting odds ratio; 95%CI= 95% confidence intervals; *numbers may not add up to 3, 361 due to missing values

DISCUSSION

We observed some similarities and differences in the RORs of the association between the global reporting of ototoxicity in VigiBase® and the parenteral use of streptomycin, amikacin, kanamycin and capreomycin for the treatment of tuberculosis. The reporting of deafness was significantly disproportionately associated with amikacin use, followed by kanamycin, but not with capreomycin use. However, for vertigo, capreomycin use was significantly associated with lower reporting odds relative to streptomycin use.

Aminoglycosides and capreomycin exhibit selective ototoxicity by damaging different parts of the inner ear, causing hearing problems (cochleotoxicity) [19,20] or postural disorders (vestibulotoxicity). [8] Amikacin, kanamycin and capreomycin predominantly cause auditory damage. [2,21–24] To date, there is no firm evidence on the comparative risk of these three drugs in causing specific ototoxicity, especially for deafness, during tuberculosis treatment. [23] The question still remains: between amikacin, kanamycin and capreomycin, which one causes more deafness? Our findings suggest that amikacin has a greater risk of deafness than kanamycin, [25] which in turn has a greater risk of deafness than capreomycin. Peloquin *et al.* compared the incidence of deafness in patients treated for MDR-TB with amikacin, kanamycin or streptomycin and found that amikacin had a greater risk of causing deafness than kanamycin, while streptomycin had the lowest risk. [26] Although our results corroborate those of Peloquin *et al.*, they are still tentative, given the nature and limitations of the spontaneous pharmacovigilance data reported in VigiBase®, [27,28] upon which the current study was based.

Although patient age was not significantly associated with the reporting of deafness, advanced age is a known risk factor for aminoglycoside-induced ototoxicity.

This has been previously reported by Sturdy *et al.*, Peloquin *et al.* and Sedon *et al.* in their studies of aminoglycoside-induced hearing loss in tuberculosis treatment. [23,26,29] The age-related loss of hearing could be because of the apoptotic loss of the auditory sensory hair cells of the organ of Corti that is associated with advancing age. [30] Additionally, our finding of lack of association between biological sex and the

occurrence of aminoglycoside-induced ototoxicity in TB treatment is consistent with the literature. [26]

The observed geographic differences in the reporting of ototoxicity across the globe could be related to the global epidemiologic distribution of TB cases; differences in the relative use of specific aminoglycosides or capreomycin in TB treatment according to national clinical guidelines; the strength of the pharmacovigilance systems in the countries comprising the regional blocks, and the quality of ICSRs from these countries. For example, although sub-Sahara Africa has a large burden of TB, there were disproportionately too few ICSRs reported in VigiBase® from this region, presumably because of the nascent or weak pharmacovigilance systems in many of the countries in sub-Saharan Africa. [31–34] For Europe, where most countries have functional pharmacovigilance systems, most ICSRs came from the Eastern countries like Romania and the Czech Republic where the burden of TB is still high. [35,36] Asia reported the most cases of vertigo because of the predominant use of streptomycin by some of the countries in this region as reported in VigiBase®, while the Americas reported relatively more cases of deafness in VigiBase® because of the disproportionately greater use of amikacin and kanamycin compared to streptomycin or capreomycin.

We believe that our findings reflect real differences in the relative ototoxicity of these drugs in clinical practice. The findings could inform the treatment choices of clinicians and managers of TB treatment programs. Globally, amikacin and kanamycin are still an integral part of MDR-TB treatment, a disease that afflicts an estimated 480 000 people, living mostly in developing countries. [6,10] The current scaled-up use of these drugs for TB treatment drives upwards the occurrence of aminoglycoside and capreomycin-induced deafness. Therefore, measures should be put in place to mitigate the risk of developing this drug-induced deafness; otherwise, countries will begin dealing with growing numbers of people suffering from avoidable hearing disabilities.

Considering known limitations of disproportionality analysis in pharmacovigilance, [37,38] we carefully restricted our data analysis solely to those ICSRs involving the use of the study drugs specifically for Tbrelated indications. Because the treatment indications were not stated for many ICSRs, we analyzed only the subset where this information was available.

Secondly, spontaneous pharmacovigilance data often lack information on the total number of patients treated with the drug being studied; hence, we were unable to calculate event rates in the absence of denominators. [28] Besides, the existence of under- or over-reporting of suspected ADRs and missing data is a typical problem of spontaneous reporting, making it susceptible to reporting bias. [27] We could not adjust for the effect of other important variables on the reporting of ototoxicity, such as renal impairment and the cumulative doses of the studied drugs, because of a lack

of this information in the structured fields of VigiBase®. Last, too few reports for some of the subgroups diminished the power of the study.

CONCLUSIONS

The reporting of deafness in VigiBase® was mainly disproportionately associated with amikacin use, followed by kanamycin. Geographic differences in the reporting of ototoxicity could be a reflection of the global TB epidemiology; and the extent of development and level of functionality of pharmacovigilance systems of the countries in those regions. Future studies with prospective designs are needed to confirm the comparative risk and the determinants of the types of ototoxicity that occur in the long-term treatment of multidrug-resistant tuberculosis using amikacin, kanamycin and capreomycin.

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CAVEAT STATEMENT

The information reported to the Uppsala Monitoring Centre (UMC) comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug related is not the same in all cases. Second, the information in this paper does not represent the opinion of the World Health Organization or the UMC.

REFERENCES

1. Mathers C, Smith A, Concha M. Global burden of hearing loss in the year 2000. Geneva; 2001.

2. Cianfrone G, Pentangelo D, Altissimi G, Turchetta R. Pharmacological drugs inducing oto-toxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. Eur Rev Med Pharmacol Sci. 2011;15:601–36.

3. Kaplan W, Wirtz .J. Veronika, Mantel-Teeuwisse AK, Stolk P, Duthey B, Laing R. Priority Medi-cines for Europe and the World 2013 Update. Geneva, Switzerland; 2013.

4. Di Perri G, Bonora S. Which agents should we use for the treatment of multidrug-resistant Mycobacterium tuberculosis? J Antimicrob Chemother. 2004;54(3):593–602.

5. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010;10(9):621–9.

6. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland; 2008.

7. Frymark T, Leech H, Mullen R, Schooling T, Venediktov R, Wang B. Drug-induced hearing loss—Aminoglycosides. Rockville, MD; 2010.

8. Selimoglu E, Kalkandelen S, Erdogan F. Comparative vestibulotoxicity of different amino-glycosides in the Guinea Pigs. Yonsei Med J. 2003;44(3):517–22.

9. World Health Organization (WHO). Global Tuberculosis Report, 2016. Geneva, Switzerland; 2016.

10. World Health Organization (WHO). MDR-TB 2014 Update. Geneva, Switzerland; 2014.

11. Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Inf J. 2008;42:409–19.

12. Uppsala Monitoring Center. Uppsala Monitoring Centre (UMC) Website [Internet]. 2015 [cited 2015 May 4]. Available from: http://www.who-umc.org/

13. Uppsala Monitoring Center. The WHO Adverse Reaction Terminology – WHO-ART [Inter-net]. 2014 [cited 2014 Dec 15]. Available from: https://www.umc-products.com/graph-ics/28010.pdf

14. ICH. Medical Dictionary for Regulatory Activities (MedDRA) [Internet]. 2015 [cited 2015 May 4]. Available from: http://www.meddra.org/

15. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the propor-tional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519–23.

16. Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. Drug Saf. 1997;16(6):355–65.

17. Van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection is spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11(1):3–10.

18. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the dis-proportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. 2011;72(6):905–8.

19. Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryngol. 2011;2011:937861.

20. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. Antimicrob Agents Chemother. 1989;33(6):797–800.

Chapter 3.1

21. Black RE, Lau WK, Weinstein RJ, Young LS, Hewitt WL. Ototoxicity of Amikacin. Antimicrob Agents Chemother. 1976;9(6):956–61.

22. Reza M, Abtahi B, Gholami K. The Incidence of Amikacin Ototoxicity in Multidrug-Resistant Tuberculosis Patients. Iran J Pharm Res. 2011;10(4):905–11.

23. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. Eur Respir J. 2012;40(5):1277–86.

24. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5.

25. Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Leufkens HGM, Mantel-Teeuwisse AK. Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. BMC Pharmacol Toxicol. BioMed Central; 2015;16(1):36.

26. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis. 2004;38(11):1538–44.

27. Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013;4(Suppl 1):S66-72.

28. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: Complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75–81.

29. Sturdy A, Goodman A, José RJ, Loyse A, O'Donoghue M, Kon OM, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. J Antimicrob Chemother. 2011;66(8):1815–20.

30. Raphael Y. Cochlear pathology, sensory cell death and regeneration. Br Med Bull. 2002;63(1):25–38.

31. Appiah B. Africa struggles to improve drug safety. Can Med Assoc J. Canadian Medical Association; 2012;184(10):E533–4.

32. Strengthening Pharmaceutical Systems Program (SPS). Safety of medicines in sub-Saharan Africa: Assessment of pharmacovigilance systems and their performance. Arlington, Virginia; 2011.

33. Maigetter K, Pollock AM, Kadam A, Ward K, Weiss MG. Pharmacovigilance in India, Uganda and South Africa with reference to WHO's minimum requirements. Int J Heal Policy Manag. 2015;4(5):295–305.

34. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance Activities in 55 Low- and Middle-Income Countries. Drug Saf. 2010;33(8):689–703.

35. Walls T, Shingadia D. The epidemiology of tuberculosis in Europe. Arch Dis Child. BMJ Group; 2007;92(8):726–9.

36. Furin J, Isaakidis P. The tuberculosis emergency in eastern Europe. Lancet HIV. Elsevier; 2016;3(3):e107–8.

37. Waller P, van Puijenbroek E, Egberts A, Evans S. The reporting odds ratio versus the proportional reporting ratio: "Deuce." Pharmacoepidemiol Drug Saf. 2004;13(8):525–6.

38. De Boer A. When to publish measures of disproportionality derived from spontaneous reporting databases? Br J Clin Pharmacol. 2011;72(6):909–11.

Chapter 3.2

Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort

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ABSTRACT

Background: Amikacin and kanamycin are mainly used for treating multidrug-resistant tuberculosis (MDR-TB), especially in developing countries where the burden of MDR-TB is highest. Their protracted use in MDR-TB treatment is known to cause dose-dependent irreversible hearing loss, requiring hearing aids, cochlear implants or rehabilitation. Therapeutic drug monitoring and regular audiological assessments may help to prevent or detect the onset of hearing loss, but these services are not always available or affordable in many developing countries. We aimed to compare the cumulative incidence of hearing loss among patients treated for MDR-TB with amikacin or kanamycin-based regimens, and to identify the most-at-risk patients, based on the real-life clinical practice experiences in Namibia.

Methods: We conducted a retrospective cohort study of patients treated with amikacin or kanamycin-based regimens in four public sector MDR-TB treatment sites in Namibia between June 2004 and March 2014. Patients were audiologically assessed as part of clinical care. The study outcome was the occurrence of any hearing loss. Data were manually extracted from patients' treatment records. We compared proportions using the Chi-square test; applied stratified analysis and logistic regression to study the risk of hearing loss and to identify the most-at-risk patients through effect-modification analysis. A P-value < 0.05 was statistically significant.

Results: All 353 patients had normal baseline hearing, 46 % were HIV co-infected. Cumulative incidence of any hearing loss was 58 %, which was mostly bilateral (83 %), and mild (32 %), moderate (23 %), moderate-severe (16 %), severe (10 %), or profound (15 %). Patients using amikacin had a greater risk of developing the more severe forms of hearing loss than those using kanamycin (adjusted odds ratio (OR) = 4.0, 95 % CI: 1.5–10.8). Patients co-infected with HIV (OR = 3.4, 95 % CI: 1.1–10.6), males (OR = 4.5, 95 % 1.5–13.4) and those with lower baseline body weight (40–59 kg, OR = 2.8, 95 % CI: 1.1–6.8), were most-at-risk of developing hearing loss.

Conclusion: Amikacin use in the long-term MDR-TB treatment led to a higher risk of occurrence of the more severe forms of hearing loss compared to kanamycin use. Males, patients with low baseline body weight and those co-infected with HIV were most-at-risk. MDR-TB treatment programmes should consider replacing amikacin with kanamycin and strengthen the routine renal, serum therapeutic drug levels and audiometric monitoring in the most-at-risk patients treated with aminoglycosides.

INTRODUCTION

Amikacin and kanamycin belong to a group of antibiotics called aminoglycosides, which are used in the treatment of Gram-negative bacterial and mycobacterial infections. These aminoglycosides, in combination with fluoroquinolones, form the backbone for the treatment of multidrug-resistant tuberculosis (MDR-TB), as recommended by the World Health Organization (WHO). [1–3] A major safety concern of the aminoglycosides is their ability to induce ototoxicity, especially during their long-term use in MDR-TB treatment. [4–6] Depending on the part of the inner ear that is affected as well as the selectivity of the aminoglycoside, the ototoxicity could be auditory or vestibular. [7] The current study focusses on the auditory toxicity (hearing loss or deafness) caused by amikacin and kanamycin. Aminoglycoside-induced hearing loss is permanent, although in some cases; it may be alleviated by the use of hearing aids, cochlear implants or speech rehabilitation, which unfortunately, are costly interventions. By experiencing hearing loss, patients end-up suffering from a distressful yet preventable drug-related disability that may negatively impact on their quality of life and limit their capability to work, for example, in occupations where good hearing ability is a requirement. In children, speech development may be severely compromised. [8]

Aminoglycosides have a narrow therapeutic index; hence require careful monitoring of serum levels, particularly during their prolonged use in MDR-TB treatment, to prevent the occurrence of dose-dependent ototoxicity. [9,10] In addition, regular audiologic assessments may help in the early detection of hearing impairment, before the damage becomes extensive and irreversible. [11–13] Some patients are genetically predisposed to suffering from aminoglycoside-induced hearing loss and genetic typing may be useful in identifying such patients. [14–17] Yet many patients in developing countries do not have access to such interventions or cannot afford them, due to weak public sector health systems and high levels of poverty.[18]

Namibia is a developing country situated in the south-western part of Africa. It is classified by the World Bank as an upper middle income country. [19] At the time of this study, there were 13 regional centers for treating patients diagnosed with MDR-TB. One of the centers - the Walvis Bay MDR-TB treatment site - began assessing patients for aminoglycoside-induced hearing loss in 2004. In 2008, Namibia changed the preferred aminoglycoside for MDR-TB treatment from amikacin to kanamycin - which was cheaper and more readily available—and introduced capreomycin as an option for patients prone to hearing loss. Later in the same year, other MDR-treatment sites commenced the systematic audiometric monitoring of patients on MDR-TB treatment for the early detection and management of aminoglycoside-induced hearing loss. The change from amikacin to kanamycin; and the introduction of systematic audiometry provided us with the opportunity of comparing the incidence of hearing loss in patients

treated with amikacin and kanamycin-based MDR-TB regimens respectively, in real-life programmatic conditions.

Even though amikacin and kanamycin have been in clinical use for over 50 years, surprisingly to-date, the evidence on their comparative risk of inducing hearing loss is scarce. Moreover, studies often have not been well done, especially in terms of measuring the hearing loss and patients with human immunodeficiency virus (HIV) co-infection have been underrepresented [6]. In sub-Sahara Africa, where the HIV and TB burden are still high, [20,21] HIV co-infection becomes a key consideration in the successful treatment of MDR-TB. [22] Tuberculosis patients co-infected with HIV are an important subgroup because of the potential effect of HIV and antiretroviral treatment on hearing function. [23–27]

The aim of this study was to compare the cumulative incidence of hearing loss among patients treated for MDR-TB using amikacin or kanamycin-based regimens, and to identify those that were most-at-risk. The high prevalence of HIV co-infection among patients diagnosed with MDR-TB in Namibia during the period of the study also enabled us to examine the influence of HIV infection on the risk of aminoglycoside-induced hearing loss.

METHODS

Study design and setting

We conducted a retrospective cohort study of MDR-TB patients treated with amikacin or kanamycin-based regimens between June 2004 and March 2014 at four public sector MDR-TB treatment sites in Namibia. Our study included the four high burden sites that collectively treated over 70 % of the MDR-TB cases in Namibia, during the study period. These were the Katutura, Oshakati, Rundu, and Walvis Bay MDR-TB treatment facilities.

Study population and sample description

The study population comprised of patients receiving treatment for MDR-TB at public sector facilities in Namibia. Our study sample included all patients who were clinically assessed and audiologically tested for hearing function at baseline and at least once, after commencing their MDR-TB treatment. Patients presenting with symptoms of hearing loss prior to the start of MDR-TB treatment were excluded from our cohort. Upon suspicion or after being diagnosed with MDR-TB infection, patients were initiated on six-to-eight months of intensive phase treatment with a regimen that contained either amikacin or kanamycin, until two sputum smears and two successive cultures turned negative for Mycobacterium tuberculosis. Thereafter, treatment was changed to the

continuous phase for 12–18 months that was administered on an outpatient basis. The average daily patient dose of amikacin or kanamycin was 15 mg per kilogram body weight, although dosing could be adjusted depending on the patient age group, weight band and renal function. [2] Patients were tested for HIV infection and, if infected, were enrolled on highly active antiretroviral treatment according to the Namibian HIV treatment guidelines that were current at that time. [28]

Study outcome

The occurrence of hearing loss after initiation of MDR-TB treatment was the main outcome of this study and was determined by an audiologist using pure tone audiometry as part of the usual care of patients treated for MDR-TB infection at the sites. Audiometry was performed at baseline, during the intensive phase of MDR-TB treatment and also in the continuation phase. No audiometry was done after completion of the MDR-TB treatment for patients who did not develop hearing loss. Hearing ability was tested by establishing the lowest intensity of sound in decibels (dB) that the person could hear at successive frequencies from 250 Hertz to 8,000 Hertz. Based on the audiogram chart provided by the Namibian Ministry of Health and Social Services (Additional file 1), the level of hearing was classified as normal (0–20 dB), mild (21–40 dB), moderate (41–60 dB), moderate-to-severe (61–80 dB), severe (81–100 dB), or profound (101–120 dB). Although the thresholds are not exactly the same, this classification of the severity of hearing loss is similar to the one provided by the American Speech-Language-Hearing Association (ASHA). [29]

   The potential confounders or effect modifiers of the aminoglycoside exposure and hearing loss relationship were patients' baseline age and weight, sex, renal function, HIV status, year of treatment initiation and the treatment site. Since capreomycin was reserved for use in patients considered at risk of developing hearing loss at the start, or at any time in the course of the intensive phase of the MDR-TB treatment, its use was not included in our study, to guard against confounding by indication of this drug.

Data abstraction and processing

Data were abstracted from clinical records using a structured form, single-entered into Epi Info™ Version 7.1.4 software (July 2014; Centers for Disease Control and Prevention, Atlanta, GA, USA) and the accuracy of entry verified against the original paper forms. All patient names and other identifiers were omitted from the final dataset to protect their privacy and to ensure their confidentiality. The anonymized and de-identified patient records were analyzed and reported in an aggregate manner, except for one patient whose serial audiograms have been anonymously published.

Chapter 3.2

Data analysis

Data were summarized using descriptive statistics. We compared continuous variables using the Student's t-test and categorical variables using the Chi-square test or the Fisher exact test. We performed univariable unconditional logistic regression analysis to assess the relationship between aminoglycoside use (amikacin or kanamycin) and the occurrence of any hearing loss. We repeated the same analysis for the less severe forms of hearing loss (mild or moderate); and the more severe forms of hearing loss (moderate-to-severe, severe, or profound). We performed stratified analyses to assess effect modification by patients' age group, sex, baseline body weight band and HIV status. The Breslow-Day test of homogeneity was used to determine if the strata-specific odds ratios were similar. Multivariable logistic regression was conducted to adjust for potential confounders for variables whose P-value for the association with hearing loss was < 0.2. We used Epi Info™ Version 7.1.4 software (July 2014; Centers for Disease Control and Prevention, Atlanta, GA, USA), for the analysis.

Ethics statement

The study was approved by the institutional review board (IRB) of the Utrecht University (Reference: UP1307) and the research and ethics committee of the Namibian Ministry of Health and Social Services, (MoHSS), (Reference: 17/3/3). A waiver of the requirement for informed consent from the patients was requested from the IRB and the MoHSS, because the study involved the review and analysis of clinical data that are routinely collected as part of the usual medical care of patients being treated for MDR-TB in Namibia. All patient names and other identifiers were omitted from the final dataset to protect their privacy and to ensure their confidentiality.

RESULTS

There were 353 patients whose records were retrieved, all of whom had documented normal hearing at the start of their tuberculosis treatment. Fifty one (14 %) of the patients were treated with amikacin-based regimens and 302 (86 %) with kanamycin-based regimens. There were 164 patients (46 %) who were HIV co-infected, of whom 132 (80 %) were on highly active antiretroviral treatment. These patient characteristics were comparable between the amikacin and kanamycin-exposed groups (Table 1).

Subsequently, during the course of their MDR-TB treatment, 206 of the patients (58 %) developed hearing loss of any severity grading (Fig. 1 and Table 2). The hearing loss was mild in 32 % of the patients, moderate (23 %), moderate-severe (16 %), severe (10 %), or profound (15 %) as shown in Table 2. Two-thirds (66 %) of the patients with

audiometrically confirmed hearing damage needed to be fitted with an hearing aid or to undergo speech rehabilitation.

Table 1: Baseline characteristics of the patients, by aminoglycoside exposure

	All Cases (N=353)		
	Amikacin (n=51)	Kanamycin (n=302)	*P*- value
Age (years): mean ± SD	35.69±9.56	36.47±11.57	P=0.85
Body weight (kgs): mean ± SD	49.58±8.83	50.76±12.0	P=0.77
Sex:			
Male, n (%)	32 (63%)	166 (55%)	P=0.47
Female, n (%)	19 (37%	136 (45%)	
HIV co-infection: n (%)	25 (49%)	139 (46%)	P=0.53
DR-TB site:			
Katutura	0	46 (15%)	
Oshakati	1 (2%)	65 (22%)	P<0.001
Rundu	0	67 (22%)	
Walvis Bay	50 (98%)	124 (41%)	
Reporting period:			
2004 – 2009, n (%)	45 (88%)	48 (16%)	P<0.001
2010 – 2011, n (%)	4 (8%)	61 (20%)	
2012, n (%)	1 (2%)	112 (37%)	
2013 – 2014, n (%)	0	80 (27%)	
Missing, n (%)	1 (2%)	1 (0.3%)	

SD=standard deviation; IQR=interquartile range; HIV=Human immunodeficiency virus
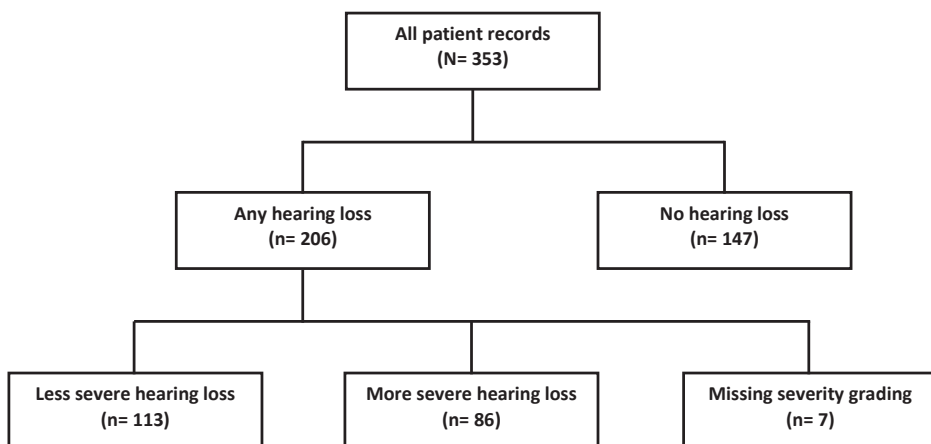
Figure 1: Study flow diagram depicting the presence or absence of hearing loss, by severity, in patients treated for MDR-TB

Table 2: Amikacin versus kanamycin use in MDR-TB treatment and the presence or absence of hearing loss

Aminoglycoside exposure	Any hearing loss	No hearing loss	Total
Kanamycin	168 (56%)	134 (44%)	302
Amikacin	38 (75%)	13 (25%)	51
Total	206	147	353

The hearing loss was sensorineural and predominantly bilateral (83 %), always beginning with high frequency loss (4–8 kHz), and then progressing to involve the lower frequencies (0.25–3 kHz) that are used for speech and conversation as shown in one of the patient's audiogram in Fig. 2. Patient X was a 36 years old male, weighing 53 kg at the start of MDR-TB treatment. His treatment regimen for the intensive phase contained amikacin, ethambutol, ethionamide and pyrazinamide. The patient began experiencing loss of hearing after about four months of treatment with this regimen. Amikacin was stopped, but the patient continued experiencing the hearing loss after the cessation of amikacin. He later developed profound hearing loss long after treatment with amikacin was stopped.
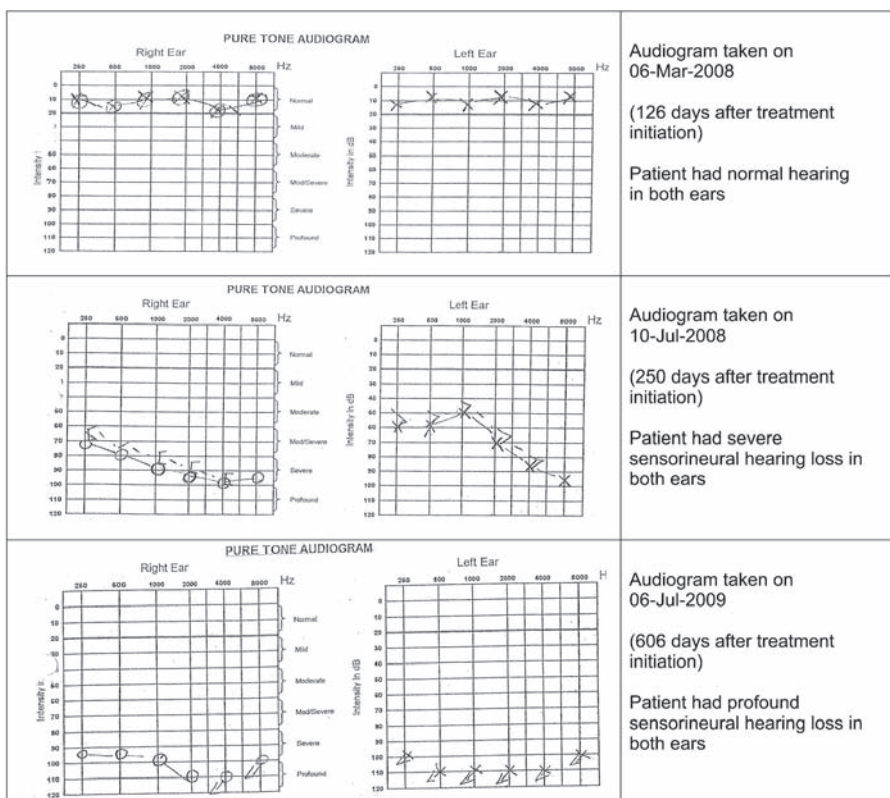
Figure 2: Serial audiograms for patient X, who developed profound hearing loss during MDR-TB treatment

The cumulative incidence of any hearing loss was greater among patients treated with amikacin-based regimens than in those treated with kanamycin-based regimens (75 % versus 56 %, p = 0.01), (Table 3), and the difference was largest for profound hearing (amikacin, 22 % versus kanamycin, 7 %, p = 0.01). Patients treated with amikacin had more than twice the odds of kanamycin of developing any hearing loss (crude odds ratio (OR) = 2.3; 95 % CI 1.2–4.6), although the confidence interval for the odds ratio for the association became wider after adjusting for confounders (adjusted OR = 2.3; 95 % CI 1.0–5.4) as shown in Table 4. When the severity of the hearing loss was taken into consideration, patients treated with amikacin had a significantly greater risk of experiencing the more severe forms of hearing loss (adjusted OR = 4.0, 95 % CI: 1.5–10.8), than of developing the less severe forms (adjusted OR = 1.6, 95 % CI: 0.6–4.5).

Table 3: Relative risk of hearing loss of amikacin and kanamycin use in MDR-TB treatment

	Any hearing loss Crude OR (95% CI)	Any hearing loss *aOR (95% CI)	Less severe hearing loss *aOR (95% CI)	More severe hearing loss *aOR (95% CI)
Kanamycin	Reference	Reference	Reference	Reference
Amikacin	2.3 (1.2-4.6)	2.3 (1.0-5.4)	1.6 (0.6-4.5)	4.0 (1.5-10.8)

Legend: aOR=adjusted odds ratio; *adjusted for patient age, treatment site and year of treatment initiation; 95%CI =95% confidence interval. Note that baseline body weight band, sex, human immunodeficiency virus infection status were not adjusted for because they were potential effect-modifiers (see Table 5).

Table 4: Effect-modification of the amikacin or kanamycin exposure and the occurrence of hearing loss in MDR-TB treatment

Variable	Strata	Stratum-specific crude OR (95% Confidence Interval)	P-value (Breslow-Day test of homogeneity across strata)
Age	Age 0-24 years	2.0 (0.4-10.6)	
	Age 25-34 years	2.8 (0.8-9.2)	0.99
	Age 35-44 years	2.6 (0.8-8.2)	
	Age 45+ years	3.0 (0.4-26.4)	
Baseline body weight	Weight 18-39 kgs	NA	
	Weight 40-59 kgs	2.8 (1.1-6.8)	0.06
	Weight 60+ kgs	1.1 (0.4-3.0)	
Sex	Female	1.1 (0.4-3.0)	0.06
	Male	4.5 (1.5-13.4)	
HIV Status	HIV negative	1.7 (0.7-4.1)	
	HIV positive	3.4 (1.1-10.6)	0.33

Legend: NA= not possible to estimate due to some cells having zero values; kgs= kilograms; HIV=human immunodeficiency virus infection status

In stratified analyses by patients' age group, baseline body weight band and by HIV infection status respectively, we noticed differences in the odds ratios of the amikacin/ kanamycin and hearing loss relationship in the different strata of these variables. Although effect modification could not be statistically confirmed due to low numbers, patients co-infected with HIV (crude OR = 3.4, 95 % CI: 1.1–10.6), males (crude OR = 4.5, 95 %1.5–13.4) and those weighing 40–59 kg (crude OR = 2.8, 95 % CI: 1.1–6.8), appeared to be at higher risk of developing hearing loss (Table 5).

DISCUSSION

Adverse drug reactions are an important consideration for patients treated for MDR-TB infection where the prolonged treatment with amikacin or kanamycin is likely to result in the development of permanent hearing loss. [16] We report a high incidence of aminoglycoside-induced hearing loss, which was more frequent in patients treated with amikacin-based regimens than in those containing kanamycin. The high cumulative incidence of hearing loss (75 %) in the amikacin-exposed group in our setting is similar to the 70 % that was reported by Reza Javadi et. al.,[30] while the 56 % incidence for kanamycin is similar to the 58 % reported by Sataloff and colleagues. [31] This provides compelling evidence that amikacin is more ototoxic than kanamycin, in real-life clinical practice.

To the best of our knowledge, the current study is the first one to quantify the comparative risk of hearing loss of amikacin versus kanamycin in their real-life use for MDR-TB treatment in a low-resource setting. It builds on previous research from other settings, which suggested that amikacin was associated with a greater risk of hearing loss, but did not quantify the magnitude of that risk. [16] Our finding is corroborated by the works of Duggal and Sarkar as well as by Sturdy and colleagues. [16,18] In Duggal and Sarkar's study, seven out of 34 patients (20.6 %) treated with amikacin for MDR-TB experienced sensorineural hearing loss involving the higher frequencies while a lesser proportion of four out of 26 patients (15.4 %) treated with kanamycin experienced the same type of hearing loss. [18] Similarly, Sturdy et.al. monitored the occurrence of hearing loss in 50 MDR-TB patients, 29 of whom were treated with amikacin, 11 with capreomycin and 10 with streptomycin, and found that the use of amikacin (P = 0.02) and decreased renal function (P = 0.01) were significantly associated with the development of hearing loss. [16] Although both studies involved small numbers of patients, their findings have been crucial in elucidating on the relative ototoxicity of the aminoglycosides used in MDR-TB treatment. Considering our current findings and those of previous research, we encourage clinicians and managers of the TB control programs that are still using amikacin as the preferred aminoglycoside for

treating MDR-TB infection, to consider changing to kanamycin. Switching to kanamycin and implementing other preventive measures, will help to reduce the occurrence of aminoglycoside-induced hearing loss among patients treated for MDR-TB.

The hearing loss seen in our study was sensorineural, mostly bilateral and began by affecting higher frequencies, then progressing to lower conversational-level frequencies as the severity of deafness increased. This finding is consistent with the pathophysiology of aminoglycoside-induced hearing loss. [4,9] After parenteral administration, aminoglycosides enter the inner ear fluids of the organ of Corti and the sensory hair cells where they are thought to react with heavy metal ions to form highly reactive free radicals that damage the stereocilia of the sensory hair cells. [32,33] There is emerging evidence that the use of antioxidants like salicylates, ion chelating agents or calcium-binding proteins may prevent aminoglycoside-induced hearing loss. [15,34–37] As illustrated in the case of patient X in this paper, a patient's hearing ability could continue deteriorating even after withdrawing the aminoglycoside due to the long half-life or the sequestration of aminoglycosides in the endolymph of the cochlea canals, which continues to cause the loss of sensory hair cells long after stopping the administration of the drug. [7,38]

We, therefore, advocate for MDR-TB treatment programs to implement routine serial audiometry in patients treated with aminoglycosides even in resource constrained settings, so that patients showing early signs of hearing loss can be identified long before the damage is too late to be reversed. When the drugs for preventing aminoglycoside-induced hearing loss become licensed for clinical use, they should be readily made available to patients, as an additional means of protecting patients from developing aminoglycoside-induced hearing loss.

The risk of aminoglycoside-induced hearing loss was greatest in patients with lower baseline body weight (40–59 kg). This could be due to a drug dosing problem whereby clinicians may fail to titrate accurately the aminoglycoside doses according to individual patient body weight. Alternatively, these could be patients who were much sicker of tuberculosis disease than the heavier weighing patients. Since we are unable to ascertain the reason for this observation due to lack of data on serum drug concentrations, we recommend further studies on the long-term pharmacokinetics and pharmacodynamics of aminoglycosides in the context of MDR-TB treatment, taking into consideration patients' renal function, anthropometric and genetic characteristics.

Patients co-infected with HIV were more at risk of amikacin-induced hearing loss than the HIV uninfected ones. There is emerging epidemiologic and clinical evidence about the association between HIV infection and hearing loss. [27,38,39] However, whether antiretroviral medicines also induce hearing loss is a question that is still unanswered because of the mixed findings of previous studies. [25,26,40] Besides, the current study doesn't shed light on this question because of a lack of adequate data

Chapter 3.2

on the specific antiretroviral (ARV) drug regimens used by the patients and insufficient patient numbers, by ARV regimen. There is need for continued research in this area to better understand the effect of antiretroviral medicines on hearing ability.

Amikacin, kanamycin and other aminoglycosides are practically not metabolized by the human body and are excreted unchanged almost exclusively by glomerular filtration, hence they require the careful monitoring of their plasma levels during therapy. [41,42] Unfortunately, therapeutic drug monitoring (TDM) of the aminoglycoside plasma levels was not performed during the treatment of patients for MDR-TB infection in Namibia. This service was not available in the public sector health system in Namibia and is not available in many developing countries, [43] perhaps explaining the relatively high incidence of ototoxicity reported among patients on MDR-TB treatment in these countries. We recommend that TB treatment programs in developing countries should consider introducing routine therapeutic drug monitoring for patients treated with aminoglycosides or capreomycin, given the higher cost of correcting permanent hearing loss for the patient and the society. A comparative cost-effectiveness analysis of conducting TDM versus not doing TDM can further inform such a strategy.

Renal clearance may strongly affect the toxicity of aminoglycosides. [41,42,44] The lack of data on renal clearance for the patients included in our analysis is an important limitation of the current study. Although we retrieved the serum creatinine levels of 114 of the 353 patients from the laboratory database, the data was of no benefit to this analysis because it represented creatinine values that were measured at time points several months after the initiation of the MDR-TB treatment and baseline data were essentially missing. This, however, does not mean that clinicians in Namibia do not assess patients on MDR-TB treatment for renal function. They do so, but because of some practical challenges in the collection of data for this study, we could not retrieve all the data on serum creatinine levels for the patients in our analysis. Nonetheless, we encourage clinicians in our setting to systematically assess all patients on MDR-TB treatment, or those at the greatest risk, for renal function at baseline and over the course of the treatment, as recommended by the Namibian TB treatment guidelines. [2]

Our study was an epidemiologic one, reflecting the real-life usage of amikacin and kanamycin in routine clinical practice. Using this study design, we identified patients that were most-at-risk of developing aminoglycoside-induced hearing loss. Importantly, hearing function was assessed using audiograms, which were part of the routine clinical follow-up of patients treated for MDR-TB. However, the data on the time-to-onset of hearing loss was unreliable because of the "batching" of patients for audiometry, due to the shortage of audiologists and audiology assistants.

Due to practical limitations about the documentation of audiometry in patients treated for MDR-TB at the sites prior to 2007, we could only retrieve information on 51 patients that were treated with amikacin for the period covered by this research.

On the other hand, for kanamycin, we retrieved 302 patients, causing an imbalance in the numbers of patients exposed to amikacin and kanamycin, respectively. To assess for possible bias, the 51 patients on amikacin were checked for the risk of hearing loss against 51 randomly selected patients on kanamycin and the results were similar to those of the 353 patient sample.

There were several other limitations of this study. For example, there were too few patients in some sub-groups which limited the power of the study for multiple sub-group analyses. Besides, we were unable to collect data on other potential risk factors like the usage of antiretroviral medicines in HIV infected patients, genetic markers of ototoxicity and other unmeasured confounders including the use of other medicines known to be ototoxic.

CONCLUSION

The long-term use of amikacin in MDR-TB treatment led to a higher risk of the more severe forms of hearing loss compared to the use of kanamycin for the same indication. Males, patients with low baseline body weight and those co-infected with HIV were most-at-risk. We recommend that managers of MDR-TB treatment programmes should consider using kanamycin instead of amikacin for the treatment of MDR-TB; and invest more resources in building the capacity and skills of health care personnel for routine renal, serum therapeutic drug levels and audiometric monitoring of the most-at-risk patients treated with aminoglycosides. More research needs to be done to better understand the combined risk of hearing loss in patients concomitantly treated for MDR-TB and HIV infections. A better designed and more powered study is needed to confirm the comparative ototoxicity risk of amikacin and kanamycin; and associated risk factors.

ACKNOWLEDGEMENT

Chapter 3.2

REFERENCES

1. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland; 2008.
2. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 3rd ed. Windhoek: MoHSS; 2012.
3. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010;10(9):621–9.
4. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. Antimicrob Agents Chemother. 1989;33(6):797–800.
5. Cianfrone G, Pentangelo D, Altissimi G, Turchetta R. Pharmacological drugs inducing oto-toxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. Eur Rev Med Pharmacol Sci. 2011;15:601–36.
6. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. Eur Respir J. 2012;40(5):1277–86.
7. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des. 2007;13(1):119–26.
8. Olusanya BO, Neumann J, Saunders JE. The global burden of disabling hearing impairment : a call to action. Bull World Health Organ. 2014;92(5):367–73.
9. Black RE, Lau WK, Weinstein RJ, Young LS, Hewitt WL. Ototoxicity of Amikacin. Antimicrob Agents Chemother. 1976;9(6):956–61.
10. World Health Organization (WHO). Report of an informal consultation on strategies for prevention of hearing impairment from ototoxic drugs. Geneva, Switzerland; 1994.
11. Jacob LCB, Aguiar FP, Tomiasi AA, Tschoeke SN, Bitencourt RF De. Auditory monitoring in ototoxicity. Braz J Otorhinolaryngol. 2006;72(6):836–44.
12. Singh Chauhan R, Saxena RK, Varshey S. The role of ultrahigh-frequency audiometry in the early detection of systemic drug-induced hearing loss. Ear Nose Throat J. 2011;90(5):218–22.
13. Fausti SA, Wilmington DJ, Helt P V., Helt WJ, Konrad-Martin D. Hearing health and care: The need for improved hearing loss prevention and hearing conservation practices. J Rehabil Res Dev. 2005;42(4s):45.
14. Bardien S, de Jong G, Schaaf HS, Harris T, Fagan J, Petersen L. Aminoglycoside-induced hearing loss : South Africans at risk. South African Med J. 2009;99(6):440–1.
15. Perletti G, Vral A, Patrosso MC, Marras E, Ceriani I, Willems P, et al. Prevention and modula-tion of aminoglycoside ototoxicity (Review). Mol Med Rep. 2008;1(1):3–13.
16. Sturdy A, Goodman A, José RJ, Loyse A, O'Donoghue M, Kon OM, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in prac-tice. J Antimicrob Chemother. 2011;66(8):1815–20.
17. Verdel BM, van Puijenbroek EP, Souverein PC, Leufkens HGM, Egberts ACG. Drug-related nephrotoxic and ototoxic reactions : a link through a predictive mechanistic commonality. Drug Saf. 2008;31(10):877–84.
18. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5.
19. World Bank. Namibia Data [Internet]. 2015 [cited 2015 Jul 18]. Available from: http://data.worldbank.org/country/namibia
20. UNAIDS. UNAIDS report on the global AIDS epidemic 2013. UNAIDS Global Report, 2013. Geneva, Switzerland: UNAIDS; 2013.

21. World Health Organization (WHO). Global Tuberculosis Report, 2014. Geneva, Switzerland; 2014.

22. Venkatesh KK, Swaminathan S, Andrews JR, Mayer KH. Tuberculosis and HIV co-infection: screening and treatment strategies. Drugs. 2011;71(9):1133–52.

23. Monte S, Fenwick JD, Monteiro EF. Irreversible ototoxicity associated with zalcitabine. Int J STD AIDS. 1997 Mar;8(3):201–2.

24. Rey D, L'Héritier A, Lang J. Severe Ototoxicity in a Health Care Worker Who Received Postexposure and Nevirapine after Occupational Exposure to HIV. Clin Infect Dis. 2002;34:418–9.

25. Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: a report of 3 possible cases and review of the literature. Clin Infect Dis. 2001;32(11):1623–7.

26. Batista A, Vieira C, Greco DB. Otoneurological manifestations associated with antiretroviral therapy. Rev Soc Bras Med Trop. 2008;41(1):65–9.

27. Katijah K. Is there a need for ototoxicity monitoring in patients with HIV / AIDS ? African J Pharm Pharmacol. 2010;4(9):574–9.

28. Ministry of Health and Social Services (MoHSS). National Guidelines for Antiretroviral Therapy. 3rd ed. Windhoek: MoHSS; 2010. 90 p.

29. ASHA. Degree of Hearing Loss [Internet]. ASHA; [cited 2015 Oct 15]. Available from: http://www.asha.org/public/hearing/Degree-of-Hearing-Loss/

30. Reza M, Abtahi B, Gholami K. The Incidence of Amikacin Ototoxicity in Multidrug-Resistant Tuberculosis Patients. Iran J Pharm Res. 2011;10(4):905–11.

31. Sataloff J, Wagner S, Menduke H. Kanamycin ototoxicity in healthy men. Arch Otolaryngol. 1964;80:413–7.

32. Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryngol. 2011;2011:937861.

33. Szczepanik W, Kaczmarek P, Jezowska-Bojczuk M. Oxidative activity of copper(II) complexes with aminoglycoside antibiotics as implication to the toxicity of these drugs. Bioinorg Chem Appl. 2004;10(II):55–68.

34. Sha SH, Schacht J. Prevention of aminoglycoside-induced hearing loss. Keio J Med. 1997;46(3):115–9.

35. Lopez-Gonzalez MA, Guerrero JM, Torronteras R, Osuna C, Delgado F. Ototoxicity caused by aminoglycosides is ameliorated by melatonin without interfering with the antibiotic capacity of the drugs. J Pineal Res. 2000;28(1):26–33.

36. Cheng AG, Cunningham LL, Rubel EW. Mechanisms of hair cell death and protection. Curr Opin Otolaryngol Head Neck Surg. 2005;13(6):343–8.

37. Karasawa T, Wang Q, David LL, Steyger PS. Calreticulin binds to gentamicin and reduces drug-induced ototoxicity. Toxicol Sci. 2011;124(2):378–87.

38. Harris T, Bardien S, Schaaf HS, Petersen L, De Jong G, Fagan JJ. Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients. S Afr Med J. 2012;102(6 Pt 2):363–6.

39. Harris T, Heinze B. Open Access Guide to Audiology and Hearing Aids for Otolaryngologists. Cape Town: UCT; 2013. p. 1–17.

40. Schouten JT, Lockhart DW, Rees TS, Collier AC, Marra CM. A prospective study of hearing changes after beginning zidovudine or didanosine in HIV-1 treatment-naïve people. BMC Infect Dis. 2006;6(28):1–6.

Chapter 3.2

41.   Pechere J-C, Dugal R. Clinical Pharmacokinetics of Aminoglycoside Antibiotics. Clin Phar-
       macokinet. 1979;4(3):170–99.

42.   de Jager P, Altena R Van. Hearing loss and nephrotoxicity in long-term aminoglycoside. Int
       J Tuberc Lung Dis. 2002;6(7):622–7.

43.   Nwobodo N. Therapeutic drug monitoring in a developing nation: a clinical guide. JRSM
       Open. 2014;5(8):2054270414531121.

44.   Prayle A, Watson A, Fortnum H, Smyth A. Side effects of aminoglycosides on the kidney, ear
       and balance in cystic fibrosis. Thorax. 2010;65(7):654–8.

Chapter 3.3

Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with tenofovir for HIV

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ABSTRACT

Background: To compare renal insufficiency among multidrug-resistant TB (MDR-TB) patients treated with kanamycin (Km)-based regimens with those concomitantly treated with Tenofovir Disoproxil Fumarate (TDF) or other antiretroviral therapy (ART) regimens in Namibia.

Methods: Retrospective review of treatment records and laboratory tests of patients initiated on MDR-TB treatment (January-December 2014). The pre/post-treatment estimated glomerular filtration rates (eGFR) were compared using ANOVA-test. Renal insufficiency was defined as an eGFR of less than 60 ml/min/1.73 m^2. Km or TDF use and renal insufficiency was assessed using Kaplan Meier plots and Cox proportional hazards analysis.

Results: The baseline mean eGFR for the three groups was the same (p=0.24); 139.3±25.6 ml/min for the Km group (n=68), 131.1±25.7 ml/min for the Km+TDF group (n=44), and 134.2±34.4 ml/min for the Km+other group (n=23). After 8 months, the values had significantly declined to 104.8±37.5 ml/min (p<0.001); 101.5±38.3 ml/min (p<0.001) and 111.5±41.7 ml/min (p=0.01), respectively. Co-treatment with Km+TDF versus Km-only regimens was associated with an elevated but not significant risk of renal insufficiency (HR=1.8; 0.7-4.1, p=0.20).

Conclusion: Renal function declined at a similar rate in MDR-TB patients treated with Km-based regimens alone compared to patients concomitantly treated with Km and TDF-based ART, or Km and other antiretroviral-based regimens.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) and the human immunodeficiency virus (HIV) infection are currently prevalent in many low and middle income countries (LMIC) where they increasingly affect the same person. [1][2] Patients co-infected with MDR-TB and HIV require complex treatment regimens that comprise of multiple anti-TB and antiretroviral (ARV) medicines. [3] These medicines are taken for long periods of time, which potentially increases the patients' risk of experiencing adverse effects; especially when the treatment regimens are administered concomitantly. [4]

For the majority of LMIC, the treatment of MDR-TB and HIV uses a public health approach in which standard regimens that constitute combinations of recommended medicines are administered to large numbers of patients. [5–7] In 2014, Km was the recommended aminoglycoside for the intensive phase of MDR-TB treatment in Namibia, in combination with a minimum of four other anti-TB drugs. [8] Similarly, Tenofovir Disoproxil Fumarate (TDF), which is a nucleotide analogue ARV used in combination with lamivudine and efavirenz, was the recommended first-line antiretroviral therapy (ART) for the treatment of HIV infection. [9] While Km and TDF are generally well tolerated, acute renal failure is a potential adverse effect of both medicines [10,11], which limits their medical use in patients with MDR-TB and HIV infection. This is because the concomitant use of Km and TDF raises the clinical concern of possible additive drug-induced nephrotoxicity. [4] Consequently, clinicians and national treatment guidelines have cautioned against the concomitant administration of aminoglycosides and TDF, [8][12] but there is limited published data from real-life programmatic experience about the concurrent use of these drugs that could guide clinicians on how best to manage patients concomitantly treated with regimens containing Km and TDF.

The aim of the current study was to compare renal function and the incidence of renal insufficiency among patients treated with standard kanamycin-based MDR-TB regimens, with those concomitantly treated with standard TDF-based ART regimens for HIV.

METHODS

Study population and study design

This was a retrospective follow up study using linked electronic treatment and laboratory patient records. All HIV-infected patients who were treated for MDR-TB between January 1st and December 31st, 2014 at Namibia's public health facilities and whose records were available in the electronic MDR-TB treatment register, the ARV dispensing register and the national laboratory database were included in the study. The datasets

contained records of patients who were consecutively enrolled for MDR-TB treatment; those treated for HIV; and the biomedical tests performed. After being on MDR-TB treatment for at least seven days, the patients were followed up forward. The study end points included diagnosis of renal insufficiency, death; or when 8 months elapsed. Patients who defaulted from care or who transferred out without reaching endpoints were administratively censored and contributed patient follow up times up to the last date of their follow up.

Records linkage and data collection

Using the LinkPlus® software (http://www.cdc.gov/cancer/npcr/tools/registryplus/lp.htm), electronic patient records in the MDR-TB treatment database, the medical laboratory tests database and the HIV treatment database were linked as was described by Corbel *et al.* [13] The final dataset contained patient's demographic data, baseline and follow-up serum creatinine data, and information about the patients' MDR-TB and HIV treatment. The time since the start of MDR-TB treatment was denoted in days. The number of days was then transformed into months of follow-up.

Medicine exposure definition

Primary drug exposure was defined as the prescription of Km according to the Namibian MDR-TB treatment guidelines. Concomitant ART exposure was defined as the dispensing of TDF or other ARVs, along with the MDR-TB treatment. The usual prescribed dose of Km was 15 mg per kilogram of body weight per day, while the standard dose for TDF was 300mg/day. Km was administered for the duration of the intensive phase of the MDR-TB treatment (lasting 8 months), while TDF is life-long, unless otherwise changed or stopped by the doctor or abandoned by the patient. The standard MDR-TB regimens for the intensive phase comprised of kanamycin, cycloserine, ethionamide, levofloxacin and pyrazinamide; and sometimes, ethambutol. Tenofovir was co-prescribed with lamivudine and efavirenz or nevirapine for HIV. The use of other reverse transcriptase inhibitor nucleoside analogues such as zidovudine (AZT) and stavudine (D4T) was recorded too. The duration that a patient had been on ART at the time of MDR-TB treatment initiation was determined.

Study endpoint definition

The study primary endpoint was the occurrence of renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m². We calculated patients' estimated glomerular filtration rate (eGFR) values from their serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (http://nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units-ckd-epi.asp). The CKD-EPI equation does not require patients' weight because the results are

reported normalized to 1.73 m² body surface area, which is the accepted average adult surface area.[14]

Statistical analysis

Patients' baseline characteristics were summarized using means (±standard deviations), medians, interquartile ranges (IQRs) and proportions. The Chi-square test and the Kruskal-Wallis test were used to assess whether the categorical variables differed significantly. The mean eGFR values were compared before and after the start of MDR-TB therapy and between the two treatment groups using a two-way Analysis of Variance (ANOVA). Kaplan-Meier survival analysis and the log-rank test were performed to compare the cumulative incidence of renal insufficiency in each group. The Cox proportional hazards analysis was used to calculate the Hazard Ratios (HRs) associated with the occurrence of renal insufficiency during the follow-up period. A p value < 0.05 was considered statistically significant.

All statistical analyses were performed using Epi Info ™ version 7.1.3.3 (US Centers for Disease Control and Prevention (CDC), Atlanta GA 30329-4027), Microsoft Excel® 2003 (Microsoft Corporation, Redmond, WA), and the EZR package of the R statistical software (EZR version 1.32).[15]

Ethics statement

This study was approved by the institutional review board (IRB) of Utrecht University (Reference: UP1307) and the research and ethics committee of the Namibian Ministry of Health and Social Services (Reference: 17/3/3).

RESULTS

Out of the 157 patient records that were retrieved from MDR-TB treatment register, 135 met the study inclusion criteria (Figure 1). Sixty-eight patients were treated with kanamycin-based regimens alone (Km group); 44 were co-treated with Km plus TDF-based ART (Km+TDF group); while 23 were co-treated with Km plus zidovudine (AZT) - or stavudine (D4T)-based ART (Km+Other group). The overall mean age was 34.8 ± 12.9 years and it was not statistically different across the three groups (p=0.25). The proportion of males in the groups was similar (p=0.20). The patients were followed up for a median of 213 days (interquartile range 150-240) from the time they initiated their MDR-TB treatment. The length of follow-up did not show statistical difference (p=0.10) across the treatment groups (Table 1). Testing for serum creatinine tended to be more frequent for the HIV co-infected persons (median 10 and 12 respectively) compared to the median of 4 tests for the uninfected persons (p<0.01).

Chapter 3.3
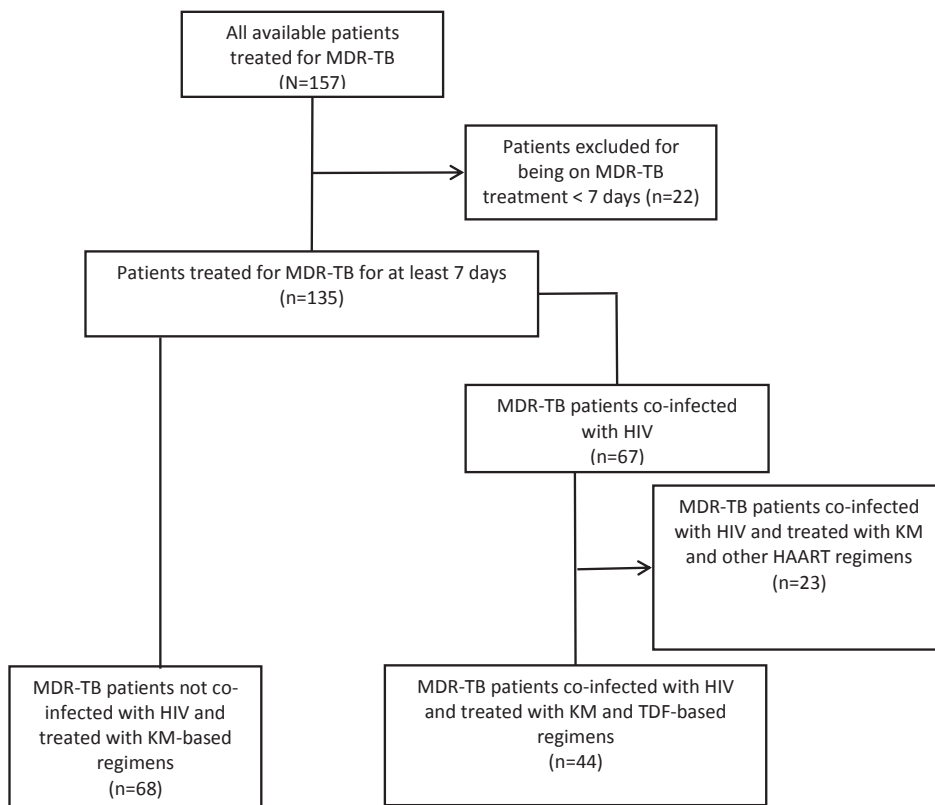
Figure 1: Study flow diagram

Table 1: Patients' baseline characteristics

Characteristic	Km group (N=68)	Km + TDF (N=44)	Km + Other* (N=23)	p value
Age in years; mean ± SD	33.8 ± 12.8	37.7 ± 13.4	37.0 ± 10.4	0.25[1]
Males, n (%)	46 (67.6%)	23 (52.3%)	16 (69.6%)	0.20[2]
Days of follow-up; median (IQR)	220 (150-240)	213 (150-240)	200 (146-240)	0.10[3]
Serum creatinine tests/ person; median (IQR)	4 (2-7)	10 (6-15)	12 (6-20)	<0.01[3]
Baseline serum creatinine (mmol/L); mean ± SD	63.7 ± 22.7	64.4 ± 17.6	66.2 ± 21.5	0.88[1]
Baseline creatinine clearance (mL/min); mean ± SD	139.3 ± 25.6	131.1 ± 25.7	134.2 ± 34.4	0.24[1]
Years on antiretroviral treatment; median (IQR)	N/A	3.5 (2-5.5)	7 (5-9)	<0.01[3]

*This sub-group comprises 23 human immunodeficiency virus (HIV) co-infected patients on zidovudine (AZT) or stavudine (D4T) based highly active antiretroviral therapy (HAART); SD=standard deviation; IQR=interquartile range; mmol=millimoles; L=litre; mL=milliliter; min=minute; N/A= not applicable;[1]ANOVA test; [2]Chi-square test; [3]Kruskal-Wallis test

At baseline, i.e. at the start of MDR-TB treatment, the 67 patients on HIV treatment had been on ART for a median of 4.0 years (interquartile range (IQR) 3.0-6.5 years). Those on TDF-based regimens had been on ART for a significantly shorter length of time compared to those on AZT/D4T-based regimens i.e. a median of 3.5 years (IQR: 2.0-5.5 years) for the TDF group versus 7.0 years (IQR: 5.0-9.0) for the AZT/D4T group, $p < 0.01$.

There was an overall gradual decline in renal function over time Figure 2. At the start of Km treatment, the mean baseline eGFR for the Km group (139.3±25.6 ml/min), for the Km+TDF group (131.1±25.7 ml/min), and for the Km+Other (134.2±34.4 ml/min), and were not statistically different (p=0.24). After 8 months of follow-up, the mean eGFR values had significantly declined to 104.8±37.5 ml/min in the Km group (p<0.001), 101.5±38.3 ml/min in the Km+TDF group (p<0.001) and to 111.5±41.7 ml/min in the Km+Other group (p=0.01), as shown in Table 2.
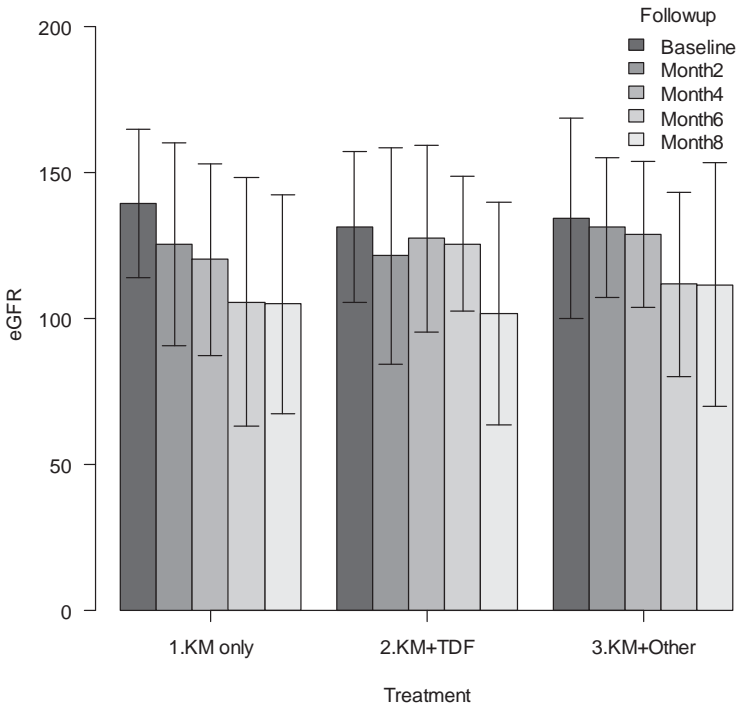
Figure 2: Renal function over time, disaggregated by patient treatment group. Km=kanamycin; TDF=Tenofovir

Chapter 3.3

Table 2: Renal function by MDR-TB treatment group before and after follow-up

	BEFORE Baseline mean eGFR (ml/min)	AFTER Mean eGFR After 8 months (ml/min)	*Within Group Difference* in mean eGFR (*p*-value)
KM only group	139.3 ± 25.6	104.8 ± 37.5	34.0 (*p*<0.001)
KM+TDF group	131.1 ± 25.7	101.5 ± 38.3	29.6 (*p*<0.001)
KM+Other group	134.2 ± 34.4	111.5 ± 41.7	22.7 (*p*=0.01)
Between Group Difference in mean eGFR (*p*-value)	*p*=0.24	*p*=0.20	

Legend: eGFR=estimated glomerular filtration rate; ml/min=millilitres per minute; KM=Kanamycin; TDF=Tenofovir Disoproxil Fumerate; Other group was treated with zidovudine or stavudine-based regimens

From the Kaplan Meier curves in Figure 3, there was a statistically significant difference in the incidence of renal insufficiency across the three treatment groups (Logrank test, *p*=0.009). However, the Kaplan Meier curves for the Km+TDF group and the Km+Other group were remarkably close to each other, crossing over at some points, especially within the 170 days of follow-up. The incidence of renal insufficiency was 2.4 cases per 100 person-months of follow-up for the Km only group; 6.8 for the Km+TDF group; and
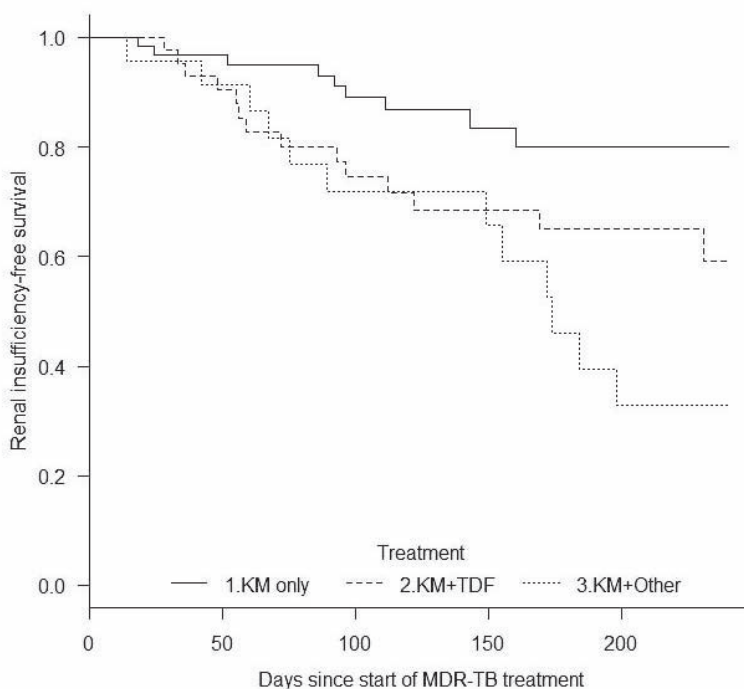
Figure 3: Kaplan-Meier curves comparing the renal insufficiency-free survival of patients by their treatment

13.8 for the Km+Other group. Taking the Km only group as the reference, the Hazard Ratio (HR) for the Km+TDF group was HR=2.1; 95% confidence interval (CI) 0.9-4.7, while it was HR=3.6; 95% CI 1.5-8.6, for the Km+Other group. When adjusted for age, the hazard ratios were HR=1.8; 95% CI 0.7-4.1, and HR=3.5; 95% CI 1.4-8.2, respectively (Table 3). Age was not a confounder but an independent risk factor.

Table 3: Factors associated with the occurrence of renal insufficiency

	Univariate analysis		Multivariate analysis	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
KM	Reference		Reference	
KM+TDF	2.1 (0.9-4.7)	0.08	1.8 (0.7-4.1)	0.20
KM+Other	3.6 (1.5-8.6)	0.004	3.5 (1.4-8.2)	0.005
Age<45 years	Reference		Reference	
Age≥45 years	2.7 (1.4-5.4)	0.004	2.6 (1.3-5.2)	0.008

KM=Kanamycin; TDF=Tenofovir; HR=Hazard Ratio; 95% CI=95% Confidence Interval; N/A=Not applicable

DISCUSSION

We observed an overall statistically significant decline in renal function over time during the treatment of MDR-TB using standard Km-containing regimens. This decline occurred at a similar rate in HIV un-infected patients treated with Km-based regimens alone compared with the HIV co-infected patients that were concomitantly treated with Km+TDF or with Km+Other ARVs, during the period of MDR-TB treatment. The concomitant treatment of patients with Km and TDF was not associated with a greater decline in renal function, in comparison with all the other groups. However, the incidence rate and hazard ratios reveal an elevated but not statistically significant risk of renal insufficiency when the two drugs are taken together during the intensive phase of MDR-TB treatment.

The loss of renal function in patients treated with kanamycin or other aminoglycosides is not a new finding. It has been unequivocally established that kanamycin and the other aminoglycosides used in MDR-TB treatment are nephrotoxic. [16–18] In the same way, tenofovir has been shown to be nephrotoxic; damaging the renal proximal tubular cells, causing defective (re)absorption of solutes from the renal tubules, and thereby resulting in a Fanconi-like syndrome or severe acute tubular necrosis. [19,20] The reason why the time-course of renal function decline seem to be comparable in the Km only and the Km+TDF groups during the follow-up period could be related to possible similarities in the pathophysiologic mechanisms underlying the nephrotoxicity

Chapter 3.3

caused by the two drugs. [21,22] This needs to be further verified through comparative biomolecular studies.

The HIV co-infected MDR-TB patients in our cohort were mostly treatment-experienced, having been on ART for a median period of about four years. Notably, those concomitantly treated with AZT or D4T-based regimens tended to have been twice as long on ART as those treated with TDF-based ART regimens. This is because AZT or D4T were adopted for ART in the public health sector of Namibia much earlier than TDF, in 2010. [23] We found that patients on AZT or D4T-based ART showed the greatest risks of renal insufficiency compared to the other treatment groups, even when the time period on ART was taken into account. We think that this could have been due to confounding by contraindication. [24] This because patients who were clinically suspected of being at risk of renal insufficiency were avoided (contraindication) from being placed on TDF-containing therapy from the year 2010 onwards. Rather, they were treated with AZT or D4T, the two drugs that were considered to be non-injurious to the kidney. The consequence of this clinical judgement was to create an inadvertent channelling effect whereby patients on AZT or D4T may falsely be seen as having renal insufficiency. This could partly explain why the Kaplan Meier curves for these two treatment groups were similar. Since we didn't have access to patients virologic and immunologic data, it was difficult for us to ascertain whether HIV-Associated Nephropathy (HIVAN) [25,26] played a role, especially given that the pattern of renal insufficiency was similar for the two types of ART regimens during the period of concomitant kanamycin treatment.

Epidemiologically, TDF exposure appears to cause only a modest decrease in eGFR,[27] with significant impairment of glomerular function being rather rare as seen in our study and that of Hall *et al.* [20] In addition, Antoniou *et al.* found that renal insufficiency was relatively rare among the 172 patients treated with TDF-based ART in their study. [28] Indeed, basing on the reviewed literature, TDF-associated nephrotoxicity is not treatment-limiting, from a public health perspective. It would appear, therefore, that the additional risk of renal failure due to the concomitant administration of Km and TDF in a real-life programmatic setting might be less than would have been theoretically expected. A bigger prospective study could help to answer this question.

A main strength of this study is that it was based on data from actual clinical practice, reflecting the real life context of the use of the study drugs. However, several potential confounding factors were not taken into account due to lack of the required data. For example, there was no information on the use of other nephrotoxic agents, on switching of antiretroviral medicines, or on the immunologic stage of HIV disease at initiation of treatment and afterwards. Moreover, it was also challenging to distinguish between ARV-related renal toxicity from HIV-associated nephropathy. Information on the exposure to medicines was only available as nominal variables - the use or non-use of the medicines of interest - thus preventing us from studying the quantitative dose

or cumulative effect of drug exposure on renal function. Being a retrospective cohort study and not a Randomised Control Trial (RCT), the study suffered from the common pitfalls of observational studies such as selection bias and confounding. Lastly, some sub-groups had few patients, thereby diminishing the power of the study to detect real differences for such sub-groups.

CONCLUSION

Renal function declined at similar rates among MDR-TB patients treated with standard Km-based regimens compared to those who were concomitantly treated for MDR-TB/HIV with Km and TDF-based ART or other antiretroviral regimens. There was an elevated but not statistically significant risk of renal insufficiency among patients who received Km+TDF as compared to those who received Km alone. Clinicians need to closely monitor renal function of MDR-TB patients on Km based treatment, irrespective of HIV status.

ACKNOWLEDGMENTS

Chapter 3.3

REFERENCES

1. Murray CJL, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. Elsevier; 2014 Jul 21;384(9947):1005–70.

2. World Health Organization (WHO). Accelerating progress on HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases. Geneva, Switzerland; 2015.

3. Venkatesh KK, Swaminathan S, Andrews JR, Mayer KH. Tuberculosis and HIV co-infection: screening and treatment strategies. Drugs. 2011;71(9):1133–52.

4. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J, Saranchuk P, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLoS One. 2012;7(7):e40781.

5. World Health Organization (WHO). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland; 2015.

6. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. Geneva; 2015.

7. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis-2011 update. 2011th ed. Geneva: WHO; 2011.

8. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 3rd ed. Windhoek: MoHSS; 2012.

9. Ministry of Health and Social Services (MoHSS). National Guidelines for Antiretroviral Therapy. 4th ed. Windhoek: MoHSS; 2014.

10. Melnick JZ, Baum M, Thompson JR. Aminoglycoside-induced Fanconi's syndrome. Am J kidney Dis. 1994;23(1):118–22.

11. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Sanchez-Niño MD, Izquierdo MC, Poveda J, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat. Hindawi Publishing Corporation; 2011;2011:354908.

12. Kenyon C, Wearne N, Burton R, Meintjes G. The risks of concurrent treatment with tenofovir and aminoglycosides in patients with HIV-associated tuberculosis. South Afr J HIV Med. NIH Public Access; 2011;12(1):43–5.

13. Corbell C, Katjitae I, Mengistu A, Kalemeera F, Sagwa E, Mabirizi D, et al. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. Pharmacoepidemiol Drug Saf. 2012;21(4):407–14.

14. National Institute of Diabetes and Digestive and Kidney Diseases. Estimating Glomerular Filtration Rate (GFR) [Internet]. Available from: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx

15. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013;48:452–458.

16. Berman LB, Katz S. Kanamycin Nephrotoxicity. Ann N Y Acad Sci. Blackwell Publishing Ltd; 2006 Dec 19;76(2):149–56.

17. Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother. 1999 May;43(5):1003–12.

18. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. QJM. 2014;107(4):261–9.

19.   Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, et al. Tenofovir-related neph-rotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis. 2003;36(8):1070–3.

20.   Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: A review of the evidence. Am J Kidney Dis. Elsevier Inc.; 2011;57(5):773–80.

21.   Paller MS. Drug-induced nephropathies. Med Clin North Am. 1990;74(4):909–17.

22.   Hoitsma AJ, Wetzels JF, Koene RA. Drug-induced nephrotoxicity. Aetiology, clinical features and management. Drug Saf. 1991;6(2):131–47.

23.   Ministry of Health and Social Services (MoHSS). National Guidelines for Antiretroviral Therapy. 3rd ed. Windhoek: MoHSS; 2010. 90 p.

24.   Joseph KS, Mehrabadi A, Lisonkova S. Confounding by Indication and Related Concepts. Curr Epidemiol Reports. Springer International Publishing; 2014 Mar 12;1(1):1–8.

25.   Röling J, Schmid H, Fischereder M, Draenert R, Goebel FD. HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy. Clin Infect Dis. Oxford University Press; 2006 May 15;42(10):1488–95.

26.   Kumar N, Perazella MA. Differentiating HIV-associated nephropathy from antiretroviral drug-induced nephropathy: a clinical challenge. Current HIV/AIDS reports. 2014.

27.   Gérard L, Chazallon C, Taburet A-M, Girard P-M, Aboulker J-P, Piketty C. Renal function in antiretroviral-experienced patients treated with tenofovir disoproxil fumarate associated with atazanavir/ritonavir. Antivir Ther. 2007;12(1):31–9.

28.   Antoniou T, Raboud J, Chirhin S, Yoong D, Govan V, Gough K, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. HIV Med. Blackwell Science Ltd; 2005 Jul;6(4):284–90.

Chapter 3.3

CHAPTER 4

General discussion

THE GROWING GLOBAL SCOURGE OF MULTIDRUG-RESISTANT TUBERCULOSIS

Tuberculosis (TB) disease is stealthily and steadily returning back. [1,2] If sufficient effort is not made in good time to control this epidemic, TB may subvert socioeconomic gains and substantially afflict humanity. [3,4] Worse still, is the unprecedented emergence and spread of drug-resistant strains of *Mycobacterium tuberculosis*, which have been observed in several countries including sub-Saharan Africa [5] and other parts of the world. [6] Multidrug-resistant tuberculosis (MDR-TB), along with other extreme forms of resistance of *M. tuberculosis*, [7–9] is a growing global menace that is seriously undermining the previous successes made in the control and elimination of TB. [10–12] In 2015 alone, there were an estimated 480,000 new cases of MDR-TB, globally, that were reported by the World Health Organization. [13] The majority of these cases were from India, China and the Russian Federation. [13] Unfortunately, the resistance of *M. tuberculosis* to current drugs is a man-made problem, mainly due to the improper use of current anti-TB drugs. [14,15] If the underlying factors that cause mycobacterial drug resistance are not adequately addressed, then the well-intentioned efforts of developing new drugs may end-up in futility, thus perpetuating a vicious cycle of drug-resistant tuberculosis in the world. Frustratingly, the global treatment success rates for MDR-TB have been poor, hovering at around 52%, [16] and varying from setting to setting depending on the design and the efforts of specific TB treatment programmes. [17,18] The backbone of current TB treatment has been the direct observation of treatment, in which a patient's dosing of prescribed anti-TB drugs is overseen and witnessed by a clinician or other designated adult. This approach is an integral feature of the WHO's directly observed treatment, short-course (DOTS) strategy, also known as TB-DOTS or DOTS-Plus for MDR-TB. [19] MDR-TB treatment may be individualized according to the specific drug sensitivity pattern of the mycobacterium, or it could be standardized according to the empirical drug sensitivity patterns prevailing in a given country. [20] The current evidence suggests that individualized MDR-TB treatments regimens are associated with slightly better treatment success rates, [21] compared to standardized regimens. [18,22] Apart from their low effectiveness, the safety and tolerability of current second-line anti-TB drugs has remained a key concern for the successful treatment of MDR-TB, because of the frequent occurrence of adverse events. [23]

This thesis aimed at investigating the real-world safety of second-line anti-TB medicines in the context of the national MDR-TB treatment program in Namibia. The research was conducted under three objectives: (i) to determine the occurrence, risk factors and clinical management of adverse events associated with MDR-TB treatment; (ii) examine the epidemiology of serious adverse events of aminoglycosides in the presence or absence of HIV infection, with or without antiretroviral therapy (ART); and (iii) assess

Chapter 4

the link between the occurrence of adverse events and patients' perception of their health-related quality of life (HRQoL) at the end of MDR-TB treatment.

In this concluding chapter, major findings of the preceding chapters are discussed, placing them in the broader perspective of MDR-TB treatment in a resource constrained setting, such as Namibia. Important recommendations for future clinical practice and research are presented. The key themes emanating from this research, as well as from other published reports, are further discussed in more detail.

SAFETY REMAINS A KEY CONCERN OF THE OLD MEDICINES FOR TREATING MDR-TB

One of the biggest therapeutic challenges that confronts the world at the moment is the lack of safer and more tolerable medicines for treating MDR-TB. [24] The current medicines for treating MDR-TB are mostly the older groups of antibiotics that are largely associated with unsatisfactory treatment outcomes [11,25,26] as well as several unpleasant side effects that make the medicines less tolerable to patients. [27] Besides, a course of treatment with typical regimens for MDR-TB involve taking a huge pill burden for a long time, which gets even more complicated in the presence of HIV co-infection [24,28] or other comorbidity. From a medical point of view, it might be a difficult challenge for clinicians if patients would choose to forgo MDR-TB treatment because of the side effects of the medicines they take since clinicians have the desire to cure patients at all costs.

Adverse events are notorious with current MDR-TB treatment regimens. [29] In **Chapter 2.1**, adverse events were confirmed to occur frequently (90%) in the majority of patients in the Namibian MDR-TB treatment program. These adverse events were of varying severity and most of them occurred during the intensive phase of MDR-TB treatment. While the majority of the patients were able to tolerate the adverse events, about 10% of them experienced serious adverse events that were potentially debilitating. Moreover, some adverse events were more prevalent among the MDR-TB patients who were co-infected with the Human Immunodeficiency Virus (HIV).

Pharmacologically, the concomitant use of two or more anti-TB drugs, plus drugs for other medical conditions by the same person opens up the possibility of clinically significant pharmacotherapeutic complications such as drug-drug interactions and additive or overlapping adverse effects. [30,31] Indeed, clinicians have been concerned about the co-administration of antiretroviral therapy and second-line anti-TB medicines in patients concurrently diagnosed with MDR-TB and HIV infection. [28] Besides, HIV disease has been shown to be associated with pathological changes that may negatively affect the treatment of MDR-TB. [32]

Consequently in **Chapter 2.2**, we compared the occurrence of adverse events among patients undergoing concomitant MDR-TB and HIV treatment, with those who were only treated for MDR-TB infection. Generally, the rate of adverse event occurrence and the associated risk factors were similar between the comorbid MDR-TB and HIV-infected (MDR-TB/HIV) patients compared with the patients who were treated for MDR-TB alone. In some instances, the presence of HIV infection appeared to modify the effects of the risk factors for the four most frequently reported adverse events that were examined in that study (tinnitus, joint pain, hearing loss, and nausea). Although the findings of the study showed a comparable risk profile of adverse event risks between MDR-TB/HIV co-infected and MDR-TB only patients, the findings were considered inconclusive because of the low statistical power of the study. In **Chapter 2.3,** it was shown that moderate-to-severe adverse events were more likely to occur and to persist among the HIV co-infected patients than among the HIV uninfected ones.

Whether second-line anti-TB medicines may be concomitantly administered with ARVs or other medicines is an ongoing debate. In South Africa, van der Walt and colleagues studied the occurrence of serious adverse drug reactions (SADRs) amongst antiretroviral naïve MDR-TB patients and found that being HIV-infected but being antiretroviral naïve did not increase the occurrence of SADRs in patients on second-line anti-tuberculosis drugs. [33] At the same time, Schnippel *et al.* reported that severe adverse events were common during the first 6 months of rifampicin-resistant TB treatment and that HIV-positive patients newly initiating ART had the highest hazard ratio for severe adverse events. [34] In India, Isaakidis *et al.* found that adverse events were frequent but rarely life-threatening or debilitating during MDR-TB treatment; and that the adverse events were not more frequent in the MDR-TB/HIV cohort than in non-HIV patients on MDR-TB treatment. [35] These, almost contradictory findings, point to the ambivalence and the inconclusiveness of the research so far reported on this subject. Various reasons could account for the differences in the findings, for example, ethnic and genetic factors or other differences in patient populations, [36–38] concomitant use of traditional or alternative medicines especially in Africa, [39–41] health system factors, [42] and so forth. Therefore, additional research in multiple countries or contexts that takes into consideration such factors will help to provide a definitive answer on the comparative risk of adverse events among patients diagnosed with MDR-TB infection only and those with concomitant HIV infection.

Often, patients diagnosed with MDR-TB face a difficult challenge in weighing the lesser evil between the MDR-TB disease itself and its treatment because of the unpleasant, sometimes intolerable, adverse effects of second-line anti-TB medicines. **Chapter 2.3** provided a background of this important issue by considering the occurrence and the clinical management of moderate-to-severe adverse events during MDR-TB treatment. Notable from this study was that moderate-to-severe adverse events are

Chapter 4

common during MDR-TB treatment. From this study, clinicians in Namibia were found to employ a number of strategies to alleviate the discomfort and to reduce the potential harm of these adverse events, in line with the Namibian TB treatment guidelines. [43] For example, the study found that clinicians may reduce the dose of the specific (suspected) offending medicine; stop, change, or replace the suspected medicine. Above all, the success of MDR-TB treatment requires the full cooperation of patients and their complete adherence to treatment, even in the face of adverse events. [17,44]

Knowing that adverse events are common and pose a challenge in MDR-TB treatment; [29,45] does the occurrence of the adverse events influence patients' perception of their health-related quality of life at the end of MDR-TB treatment? We explored this question in a paper that is presented in **Chapter 2.4**. The study revealed that patients who completed their MDR-TB treatment in Namibia tended to score moderately low on their HRQoL, using the generic SF-8™ questionnaire. No association was, however, found between the patients' HRQoL scores upon treatment completion and the occurrence of adverse events. This implies that MDR-TB may be associated with a decrement of HRQoL, irrespective of the occurrence or the non-occurrence of adverse events. In other words, it could be more of the disease itself rather than its treatment that is associated with the reduction in patients' perceived HRQoL. However, this finding needs to be confirmed in a larger study that measures HRQoL at baseline, at multiple time points during the MDR-TB treatment phases and at the completion of treatment so that the changes in HRQoL may be ascertained.

On the other hand, for MDR-TB patients co-infected with HIV, the therapeutic situation is a bit dire. Isaakidis and colleagues paint a grim picture of patients concurrently treated for both infections. The statement made by one of the patients '*I cry every day*' is particularly moving.[46] These patients find the treatment to be quite demanding to take, and for the adverse events to be intolerable. Another patient bluntly stated that the side-effects of the MDR-TB treatment were '*as bad or worse than the illness itself*'. [46] Clearly, the reaction of patients about the MDR-TB treatment experience varies from person to person. Some patients can withstand drug treatment and are able to tolerate well the adverse effects of the treatment, while others cannot. How can clinicians anticipate whether patients may cope with their MDR-TB treatment? This is not an easy task. Probably, population risk-profiling studies for tuberculosis medication might help to provide a deeper insight into this problem.

Indeed, the topic of the safety of old second-line anti-TB medicines is an important one. It is important because there are currently very limited therapeutic options of safer and more efficacious medicines for clinicians and patients to choose from. A difficult therapeutic dilemma is therefore presented on whether to continue treating patients with the old medicines that are prone to causing adverse effects and, at the same time, are not very effective in curing MDR-TB; or whether to treat patients with

newer medicines such as bedaquiline and delamanid whose safety and efficacy has not yet been fully proven in daily practice . The famous English idiom "*Better the devil you know than the angel you don't*" seems to provide an escape out of this conundrum. At the moment, it appears to be prudent to deal with the familiar old anti-TB drugs that clinicians know quite well, even if they are not ideal, than take a risk with the unknown, and yet to be fully understood new drug. This, therefore, calls for the judicious use of the old anti-TB drugs that remain the cornerstone of MDR-TB treatment. [47] In this respect, patients and their treatment supporters should be encouraged to take anti-TB medicines correctly as prescribed, until the treatment is completed. [48] The correct and complete adherence to tuberculosis treatment will vastly reduce the chances of development of drug-resistant mycobacteria.

OTOTOXICITY AND NEPHROTOXICITY: A STRONG CASE FOR NEWER, SAFER ANTI-TB DRUGS

Is it worth it to become deaf or to develop acute (or chronic) kidney disease because of MDR-TB treatment? Can the risk of aminoglycoside-induced ototoxicity and nephro-toxicity be avoided? These are hard clinical questions that hound the current MDR-TB drug therapy.

To date, amikacin, kanamycin and capreomycin are still an essential component of the intensive phase of MDR-TB treatment. [49] Unfortunately, this important category of drugs is stubbornly associated with a significant risk of developing hearing loss [50] and / or renal insufficiency. [51] In **Chapter 3.1** we found that the reporting of deafness in VigiBase® in the context of tuberculosis treatment was mainly disproportionately associated with the use of amikacin, followed by kanamycin. Also, there were notice-able geographic differences in the reporting of ototoxicity, which could be a reflection of the global TB epidemiology; as well as the extent of development and the level of functionality of pharmacovigilance systems of the countries participating in the WHO global programme for monitoring the safety of medicines.

Chapter 3.2 compared the occurrence of amikacin and kanamycin-induced hearing loss in MDR-TB treatment under programmatic conditions in a Namibian retrospective cohort. Under such conditions of real-world clinical application, the long-term use of amikacin in MDR-TB treatment was associated with a higher risk of the more severe forms of hearing loss compared to the use of kanamycin. Moreover, male patients, those with a low baseline body weight and those co-infected with HIV were most-at-risk of aminoglycoside-associated hearing loss. Consequently, we recommend that managers of MDR-TB treatment programmes should consider using kanamycin instead of amikacin for the treatment of MDR-TB. Second, national MDR-TB treatment

Chapter 4

programmes should invest more resources in building the capacity and the skills of health care personnel for the routine measurement of serum therapeutic drug levels, [52] audiologic monitoring and the of assessment of renal function of the most-at-risk patients treated with aminoglycosides. [53] In their paper, van Altena and colleagues have demonstrated that by using therapeutic drug monitoring (TDM), the risk of hearing loss can be reduced without sacrificing therapeutic efficacy when the dosage of aminoglycosides is reduced to an appropriate maximum concentration (C_{max}) to mean inhibitory concentration (MIC) ratio (C_{max}/MIC). [54] Their focus on therapeutic dosing using C_{max}/MIC ratio rather than the conventional per kilogram body weight dosing is novel and may offer a pharmacokinetic alternative for minimizing the risk of hearing loss in patients at risk. Indeed, targeted therapeutic drug monitoring of aminoglycosides during MDR-TB treatment can minimize the occurrence of otologic and nephrologic adverse effects, without compromising therapeutic success. [55–57] Therefore the capacity for therapeutic drug monitoring should be enhanced for routine use in low resourced settings, especially now that laboratory technology is becoming better, more accessible and widespread. [58] Besides, more research needs to be done to better understand the risk of hearing loss in patients concomitantly treated for MDR-TB and HIV infections. A better designed and more powered study is needed to confirm the comparative ototoxicity risk of amikacin and kanamycin; and the associated risk factors.

Renal dysfunction is another important adverse reaction that may potentially limit the usefulness of aminoglycosides and capreomycin in MDR-TB treatment. [59,60] This was discussed in detail in **Chapter 3.3** where the renal function of MDR-TB patients who were treated with kanamycin regimens or concomitantly with tenofovir for HIV infection was monitored and compared by type of treatment. In this study, renal function declined at similar rates among the MDR-TB patients who were treated with standard kanamycin-based regimens compared to those who were concomitantly treated for MDR-TB and HIV using both anti-TB and tenofovir-based antiretroviral regimens. Although not statistically significant, there was an observable excess risk of renal insufficiency among the patients who received kanamycin plus tenofovir as compared to those who received kanamycin alone. Consequently, we emphasize that clinicians need to closely monitor the renal function of MDR-TB patients on kanamycin containing regimens, irrespective of HIV status, because of the increased risk of nephrotoxicity of kanamycin.

Although MDR-TB disease may be considered as an old problem, new therapeutic solutions are urgently required. [47] Looking at the long-term safety profile of aminoglycosides and capreomycin; and considering the patient discomfort from the frequent painful injections of this category of drugs, there is a pressing need for novel, safer medicines that can be administered orally as shorter, efficacious MDR-TB regimens. [4,61] Several efforts are ongoing to achieve this goal. [27,62] So far, bedaquiline, dela-

manid and linezolid are the newer drugs that have recently been licensed for clinical use in MDR-TB treatment, [63] while pretomanid and a few other candidate molecules are still undergoing clinical trials. [27,61]

However, regulatory, logistic and financial access to the current and new anti-TB medicines remains a major barrier for MDR-TB treatment programmes in many low and middle income countries. [11,27,64–66] Interruptions in the supply of anti-TB medicines are not uncommon in most of the developing countries. [67] For the majority of these countries, access to essential medicines is a wider pharmaceutical and health system problem as was elaborated by Cameron *et al.* [68] This matter needs to be seriously addressed by health managers and managers of the public sector pharmaceutical supply chain in these countries, so that anti-TB and other essential medicines are accessible to all. Global partnerships and initiatives, such as the Global Drug Facility (GDF) are increasingly playing a pivotal role in promoting access to second-line anti-TB medicines. [69] According to Lucica Ditiu, the Executive Director of the Stop TB Partnership, "*GDF will continue to play a key role in increasing access to and scaling up the use of new anti-tuberculosis medicines, including bedaquiline and delamanid, and new paediatric formulations and the rapid introduction of shorter drug-resistant tuberculosis treatment regimens.*"

Apart from their safety concerns, second-line anti-TB drugs are costly and unaffordable for many countries and patients. [70,71] This makes MDR-TB treatment to be inaccessible to many patients. [71,72] Thus, it is crucial for innovative solutions to be implemented as part of the wider health system financing strategies for sustainably financing the procurement and supply of current and new anti-TB drugs. [73] Countries like China are looking critically into sustainable government financing and social health protection schemes to ensure universal access to appropriate TB treatment. [74,75] Indeed, universal health coverage, strong regulatory frameworks, timely registration of new medicines and formulations, quality assurance and rational use of medicines, are key components of the current End TB strategy of the WHO. [76]

Meanwhile it is important that the old drugs are used as safely as possible. Measures need to be taken to promote patient safety, which also contributes to improving the quality of care during MDR-TB treatment. Our studies provide several insights on how this may be achieved, as discussed below.

HOW CAN THE SAFETY OF CURRENT, OLD ANTI-TB MEDICINES BE OPTIMIZED IN ADULT PATIENTS?

Pending the research, development, regulatory approval and availability of new, safer anti-TB medicines, MDR-TB treatment programs need to fully optimize the safety of

Chapter 4

current medicines. The safety of current medicines for MDR-TB treatment can be optimized by focusing on the product and on the health system, particularly on pharmacovigilance. There are several strategies that could be used to achieve this. First, clinicians should closely monitor patients on MDR-TB treatment to ensure that the adverse effects of second-line anti-TB drugs are recognized as quickly as possible so that remedial measures may be taken early enough. [77,78] The ability to monitor patients for adverse effects on a daily basis is a major advantage of the directly observed therapy (DOT) strategy over the self-administration of MDR-TB treatment (SAT). [79] Fortunately, the majority of the adverse effects of second-line anti-TB drugs are easily recognizable and patients tend to freely disclose them to clinicians. [79] Nonetheless, it is important to have a systematic method for asking patients whether or not they experienced any adverse events during treatment since some patients may not be forthcoming with reporting even the severe adverse effects of their treatment. [78,80] In addition, other patients may overlook some adverse events and selectively tell the health care provider about others. [79] Once recognized, the adverse events should be properly managed, using some of the practical approaches that have been mentioned in **Chapter 2.3**.These include, but are not limited to, reducing the dose of the offending drug; stopping or substituting the suspected drug with another drug that is devoid of the adverse reaction; and using other adjunctive drugs such as antidotes or antagonists to prevent, counteract or treat the symptoms of the specific adverse reaction.

Second, the serial monitoring of hearing levels is invaluable during MDR-TB treatment. **Chapter 3.2** provides an example of how the Namibia MDR-TB treatment programme has started to conduct systematic audiologic assessments in patients. At the time of going to press, such routine assessments were not yet being widely done in all of the 13 MDR-TB sites in the country, partly because of insufficient audiologists or audiology assistants and the lack of equipment needed for audiology. The Namibian Government has since then began investing more resources to expand audiologic assessments to all the MDR-TB treatment centers.

Third, laboratory screening is another effective way for detecting certain adverse effects of second-line anti-TB drugs that are not often detectable by the patient or the DOT provider. [79] A simple schedule of monitoring key biomedical parameters, indicating the minimal recommended frequency, should be included in MDR-TB treatment guidelines. For the high-risk patients, more frequent tests may be advisable. This approach has been illustrated in **Chapter 3.3** on the monitoring of renal function of patients on MDR-TB treatment. This approach can be used for screening many other drug-associated abnormalities like electrolyte disturbances, hormonal and hepatic disorders. An integrated schedule for the laboratory monitoring of MDR-TB/HIV patients may avoid unnecessarily duplicate testing of the same laboratory variable when monitoring the treatment of MDR-TB and HIV, respectively.

Recently, there has been greater advocacy for the use of therapeutic drug monitoring (TDM) in the optimization of aminoglycosides and capreomycin in MDR-TB treatment. [54,56,57] Sotgiu *et al.* have placed a specific emphasis on the practical utility of the dried blood spot technique in collecting samples for conducting TDM in resource constrained settings. [81] In Namibia, Verbeeck and colleagues have been at the forefront of advancing the use of TDM in optimizing the dosing of aminoglycosides and other drugs in TB treatment. [82] Such advocacy needs to continue so that TB program managers dedicate more resources in using TDM to optimize drug dosing for the minimal occurrence of adverse events, while ensuring the efficacy of treatment is not compromised.

For countries with a strong laboratory infrastructure and capability; and where resources permit, individualization of MDR-TB therapy would be encouraged. [83] Individualization of therapy helps to optimize the effectiveness of current drugs while minimizing the occurrence of adverse events. [84] Apart from therapeutic drug monitoring, the use of whole genome sequencing for drug resistance testing paves the way for individualized precision medicine whereby only the drugs to which the mycobacterium is sensitive are included in the MDR-TB treatment regimen for a specific patient. [85,86] As biotechnological innovations become more affordable, they should be widely adopted and employed in the treatment of patients with MDR- or XDR-TB.

Other promising strategies that could be explored for mitigating the adverse effects of MDR-TB treatment are the pharmacologic use of antioxidants and chelating agents to protect against hearing loss; [87,88] and using adjuvants such as pyridoxine to protect against peripheral neuropathy. [89] However, the clinical use of candidate agents, such as N-acetylcysteine and others, to protect against drug-induced ototoxicity is still undergoing investigation. [90–92] For agents where the protective benefits of adjuvant therapy have been demonstrated, such medicines should always be made available along with anti-TB medicines so that they may be co-administered during MDR-TB treatment.

Another important therapeutic strategy to explore is the shortening of the length of exposure to ototoxic and nephrotoxic second-line anti-TB drugs. The STREAMS trials, seeking to find a shorter regimen for MDR-TB using currently available anti-TB drugs, have shown promising results, offering the possibility of a more acceptable and more effective regimen than the current WHO recommended regimens. [93]

Where severe ototoxicity or nephrotoxicity inevitably occurs, TB treatment programs need to provide for the disability supportive care and the rehabilitation of patients who experience these and other debilitating adverse effects of second-line anti-TB drugs. [94] Such post-treatment support will help patients to cope with the long-term adverse effects of MDR-TB treatment on their physical health and functional abilities.

Chapter 4

Finally, implementing systematic drug utilization reviews (DUR), also called drug/medicine use evaluations (DUE or MUE) in MDR-TB treatment programs may help TB program managers to promote the safer and rational use of second-line anti-TB medicines. [95] Well designed and implemented DURs contribute to improving the quality of treatment services. Prospective DURs have the inherent advantage if promptly identifying medicine use problems and correcting them immediately, thereby providing an in-built system for minimizing the consequences of adverse events during treatment. DURs are not difficult to implement, hence TB program managers are encouraged to consider adopting this strategy.

OPTIMIZING THE SAFETY AND TOLERABILITY OF SECOND-LINE ANTI-TB MEDICINES IN CHILDREN: WHAT DO WE DO FOR THEM?

Thus far, the discussion in this thesis has mainly focused on the safety of second-line anti-TB drugs in adults. Yet children represent a uniquely important group in MDR-TB treatment that warrants special attention. [96–98] The global incidence of MDR-TB among children is also on the rise, [99,100] and more children are increasingly in need of treatment with second-line anti-TB medicines. Unlike adults, children are less likely to withstand daily painful injections of aminoglycosides or capreomycin for eight months; [101] or the often unpalatable oral medicines. [102] Besides, younger children may be less articulate in describing the symptoms of the adverse events that they may experience. The occurrence of adverse events in children treated for MDR-TB using second-line anti-TB drugs has not been exhaustively studied. [103,104] Although the majority of the known adverse events that occur among children are mild or moderate, [103] the potential impact of debilitating adverse events such as hypothyroidism [105], nephrotoxicity and hearing loss [106] on a developing child could be more significant than in adults, with far-reaching consequences. [23] A study by Franck and colleagues in South Africa reported that pill burden and medication adverse effects caused considerable physical, psychological and academic disturbances in children; and that the adverse effects were important obstacles to treatment adherence. [107]

Unfortunately, there is limited information on the safety of current second-line anti-TB medicines in children because most trials have excluded children, [104] mainly for ethical reasons. [108] Secondly, paediatric dosing could be inappropriate because it is typically extrapolated from adult trials. [102] Notwithstanding the safety of most of the currently available anti-TB medicines not being studied in children during clinical trials, most of the available pharmaceutical formulations are meant for adults, with few being available in appropriate paediatric formulations. [109,110] The availability and access to oral pediatric medicines remains a huge challenge in many African countries,

[111] and globally as well. [112] It therefore, makes it extremely difficult for clinicians to effectively treat children diagnosed with MDR-TB. [113] This challenge is vividly expressed by Professor Susanna Esposito in Italy when she treated MDR-TB in an 11 year old boy called Alessandro.

> **Box 1: Quote from Professor Susanna Esposito, Italy [114]**
> "One of the challenges of treating children with TB is the availability of off-label drugs, due to their age. Furthermore, there are very few drugs available in syrup form for children that are not able to swallow pills. Another problem is that certain drugs are not available in each country, so we need adequate importation procedures that will not take too long, especially during holiday periods. For example, when we were treating Alessandro, there was an instance when his drugs had not been imported from the UK to Italy on time." – *Professor Susanna Esposito*

From the present body of literature on this subject, some broad strategies emerge for optimizing the safety and tolerability of second-line anti-TB medicines in children. [102,110,115] The first strategy is based on optimizing the currently available medicines. Pertinent to this strategy is the development of better pediatric pharmaceutical drug delivery systems [102,110] and the devising of optimal dosing schemes; [100,116] designing shorter treatment regimens of current drugs; [100,117] and developing fixed-dose combinations to reduce the pill burden in children. [110] The Global Alliance for TB Drug Development ("TB Alliance") is at the forefront of spearheading the development of simple, better tasting child-friendly formulations of old and new anti-TB medicines. [118] This includes the development of fast-dissolving palatable tablets that are pharmaceutically stable and easy to administer. [110] Such increased focus on developing and availing child-friendly formulations and the optimal dosing of old anti-TB medicines has given a fresh hope for children. [115] When new child-friendly formulations are available, they should be rapidly adopted by national TB clinical treatment guidelines for a quick uptake of the new pharmaceutical technologies. [119]

The second strategy, which moves beyond pharmaceutical dosage form improvements and regimen optimization of old medicines, is to develop novel, affordable compounds that are effective and safer for children. [102,120] There is a growing consensus to include rather than exclude children in clinical trials for developing new anti-TB medicines. [121] Advocacy groups, like the Treatment Action Group (TAG), are keeping the pressure on researchers and funders to commit more resources in developing newer, practical, child-friendly formulations of anti-TB and anti-HIV medicines. [122] It is hoped that this persistent advocacy will yield positive results in the near future.

It therefore behooves the global scientific community and funders to invest more resources into the research and development of newer, safer, more efficacious and

Chapter 4

affordable anti-TB medicines for both adults and children, which can protect humanity against this growing scourge of MDR-TB and other deadlier forms of *Mycobacterium tuberculosis* resistance. [123]

STRONGER PHARMACOVIGILANCE AND RISK MITIGATION IS ESSENTIAL FOR PROTECTING PATIENTS

The fast-tracked introduction of new anti-TB therapies compels drug regulatory authorities and national TB programmes to have in place strong pharmacovigilance systems. This is because of the safety concerns that surround the early introduction of new medicines after being licensed for medical use, based on clinical trials that were conducted in a limited number of patients and for relatively short periods of time. [124–126] Additional safety data needs to be collected through ongoing post-marketing (Phase IV) safety studies for the new drugs. [127] At the same time, in spite of drug regulatory authorities having the statutory responsibility to protect the public against ineffective and unsafe drugs, regulatory authorities also need to balance between stringent regulation and facilitating the timely access by patients to new life-saving drugs for MDR-TB or XDR-TB treatment. [128] This further underscores the importance of having robust pharmacovigilance systems in a country. Even the older anti-TB drugs should be closely monitored for the occurrence of adverse events and their safety managed from a clinical and public health point of view, through robust pharmacovigilance systems. [129] In view of this, national TB control programmes should have strong pharmacovigilance systems for monitoring, detecting, and managing the adverse events that emerge during the use of the anti-TB drugs and related medicines. [78] Further, there needs to be a seamless connection, collaboration or integration with the national pharmacovigilance systems, to aid the timely detection and characterization of medicine-associated risks, [130] which inform the design and implementation of specific risk mitigation strategies for the affected medicines. In this regard, the wider health and pharmaceutical system factors also come into play in influencing the strength and effectiveness of national pharmacovigilance systems. [131] More financial, human and material resources need to be made available to support the implementation and running of pharmacovigilance activities for TB control and other public health programs in low and middle income countries. [132,133]

To build their capacity in medicine safety management, health care workers need to be trained in pharmacovigilance. [133,134] Importantly, all directly observed TB treatment (DOT) providers, including the hospital, clinic or community health workers should be trained to screen patients regularly for symptoms of common adverse effects. [79] In Namibia, the current TB treatment guidelines require DOT providers to be trained in

simple adverse drug reaction management and on the steps for referring patients to a nurse or physician for severe and serious adverse events. [43] Towards this end, simple, easy-to-understand pictograms could be used to help patients and lay community DOT providers in identifying and describing the symptomatic adverse events that are associated with MDR-TB treatment. [135,136] Given the critical shortage of healthcare workers in most countries, information and communications technology (ICT) could be leveraged for the more efficient conduct of pharmacovigilance activities. [137,138] When possible, patient medical records should be computerized in order to improve the quality of pharmacovigilance data and to facilitate data analysis. [139]

Traditionally, pharmacovigilance systems have relied heavily on spontaneous reporting. [140] To broaden the spontaneous reporting channels and to encourage more participation, efforts are underway to promote patient involvement in the reporting of adverse events in public health programmes in low and middle income countries. [141] In the same way, an appeal has been made for pharmacists to play a bigger role in pharmacovigilance activities. [142,143] Recently, more focus is now being placed on using active surveillance strategies to complement spontaneous reporting. [80,144] There are some illustrative examples where active surveillance is being used to monitor the safety of anti-TB [145] and antiretroviral medicines in Namibia [146] and other low and middle income countries. [147,148] Such cohort monitoring-based pharmacovigilance systems, which may require more resources to implement, have been shown to be feasible in Namibia. [149] Linkage of electronic healthcare records from existing health service databases, like the ones in Namibia as was demonstrated in **Chapter 3.3**, is another way of efficiently conducting pharmacoepidemiologic studies to answer specific medicine safety questions. [150] Furthermore, encouraging attempts are being made to use social media as an additional channel for monitoring the safety of medicines through complex but highly efficient computer data mining algorithms. [151–153] This approach holds a lot of promise for the future of safety monitoring of current and new anti-TB medicines, globally.

METHODOLOGICAL CHALLENGES OF OBSERVATIONAL STUDIES OF DRUG-INDUCED ADVERSE EFFECTS IN MDR-TB THERAPY IN AFRICA

Several notable methodological challenges were encountered in the course of this research. First and foremost, despite the MDR-TB incidence being on the rise; in many settings, the absolute numbers of patients infected with MDR-TB (the prevalence), is still relatively too low. This makes it difficult to design studies with adequate statistical power for detecting rare events. An example is Namibia, where the registered number of patients diagnosed and treated for MDR-TB in 2014 was 157. [154] Consequently,

the research conducted in this thesis was constrained by sample size in its ability to examine drug exposure-event associations in sub-groups or in multivariable analyses. Moreover, the few annual incident cases of MDR-TB in the Namibian setting meant that it would have taken a much longer time to conduct a prospective follow-up study, if such an approach were to be used. To overcome this challenge, some researchers have suggested the pooling of data across countries and the application of data-mining techniques to improve the detection of drug-safety signals. [155]

Second, there were data availability and quality issues, including missing variables and incomplete data. Thus, we could not obtain information on some important co-variates of interest and on the outcomes of some of the adverse events, for example, death. A potential solution around this problem is the implementation of targeted spontaneous reporting (TSR), a method of pharmacovigilance that integrates elements from cohort event monitoring and spontaneous reporting. [156]

Another contributor to the poor availability and quality of data for pharmacovigilance in many African and other low and medium-income countries is weak health informa-tion systems. [157] Fortunately, many countries have recently begun using electronic medical records and other electronic tools, which promises to improve the availability and quality of data for pharmacovigilance and other health research. [158,159] Par-ticularly, special care should be taken to avoid using dual (electronic and paper-based) information systems in a way that may compromise data quality; [160] while adequate plans should be made for the sustainable use of electronic health systems in Africa. [161] Integrating health records between the public and private sectors through system interoperability will go a long way in facilitating country-wide pharmacoepidemiologic studies in Africa. [162]

CONCLUSION AND RECOMMENDATIONS

This thesis showed that adverse events occur frequently in patients treated with second-line anti-TB drugs. The majority of the adverse events are preventable. A few of the second-line anti-TB drugs (aminoglycosides and capreomycin) are associated with potentially debilitating nephrotoxicity and ototoxicity, which may diminish patients' health-related quality of life after taking the medicines. Besides, there may be clinically important overlapping adverse events in patients also taking antiretroviral medicines. Despite the safety and efficacy concerns with current second-line anti-TB drugs, these drugs are still needed in the treatment of MDR-TB. The focus, therefore, is on ensuring the safer use of current and new anti-TB drugs. In view of this, the current thesis has highlighted the key adverse events that occur in MDR-TB treatment and how they could be clinically managed so that current second-line anti-TB drugs are used as safely as

possible. The monitoring of adverse events should be done on regular basis throughout MDR-TB therapy. Managers of TB control programs should strengthen pharmacovigilance systems so that clinically important adverse events may be detected early and mitigation measures instituted in time, for example, through the active surveillance of adverse events. The long-term impact of adverse events on patients' health-related quality of life after completing MDR-TB treatment should be ascertained. More investment is needed in developing novel, safer and more effective anti-mycobacterial compounds; as well as child-friendly formulations. Importantly, these medicines should be made accessible to those who need them, which will contribute towards achieving universal health care coverage.

Chapter 4

REFERENCES

1. Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? Clin Microbiol Infect. Elsevier; 2013;19(10):889–901.

2. Jassal MS, Bishai WR. Epidemiology and challenges to the elimination of global tuberculosis. Clin Infect Dis. Oxford University Press; 2010;50(Supplement 3):S156-64.

3. Dirlikov E, Raviglione M, Scano F. Global tuberculosis control: Toward the 2015 targets and beyond. Ann Intern Med. 2015;163(1):52–8.

4. Raviglione M, Sulis G. Tuberculosis 2015: Burden, Challenges and Strategy for Control and Elimination. Infect Dis Rep. 2016;8(2):6570.

5. Menzies HJ, Moalosi G, Anisimova V, Gammino V, Sentle C, Bachhuber MA, et al. Increase in anti-tuberculosis drug resistance in Botswana: Results from the fourth National Drug Resistance Survey. Int J Tuberc Lung Dis. 2014;18(9):1026–33.

6. Migliori GB, Dheda K, Centis R, Mwaba P, Bates M, O'Grady J, et al. Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa. Trop Med Int Heal. 2010;15(9):1052–66.

7. Gandhi NR, Nunn P, Dheda K, Schaaf HS, Zignol M, van Soolingen D, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet. 2010;375(9728):1830–43.

8. Alexander PE, De P. The emergence of extensively drug-resistant tuberculosis (TB): TB/HIV coinfection, multidrug-resistant TB and the resulting public health threat from extensively drug-resistant TB, globally and in Canada. Can J Infect Dis Med Microbiol. Hindawi Publishing Corporation; 2007;18(5):289–91.

9. Matteelli A, Roggi A, Carvalho AC. Extensively drug-resistant tuberculosis: epidemiology and management. Clin Epidemiol. 2014;6:111–8.

10. Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest. 2006;130(1):261–72.

11. Dheda K, Limberis JD, Pietersen E, Phelan J, Esmail A, Lesosky M, et al. Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: a prospective cohort study. Lancet Respir Med. 2017;2600(16):1–13.

12. Zignol M, Dean AS, Ph D, Falzon D, Gemert W Van, Wright A, et al. Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. N Engl J Med. 2016;375:1081–9.

13. World Health Organization (WHO). Global Tuberculosis Report, 2016. Geneva, Switzerland; 2016.

14. Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. Int J Tuberc Lung Dis. 2010;14(4):382–90.

15. Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. Br Med Bull. Oxford University Press; 2005;73–74(1):17–24.

16. World Health Organization. Multidrug-resistant tuberculosis (MDR-TB). Geneva; 2016.

17. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia-an observational cohort study. Thorax. 2015;70(12):1181–8.

18. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: A systematic review and meta-analysis of published studies. Infect Dis Poverty. 2017;6(1):1–8.

19. World Health Organization (WHO). What is DOTS? A Guide to Understanding the WHO-recommended TB Control Strategy Known as DOTS. Maher D, Mikulencak M, editors. Geneva: WHO; 1999.

20. World Health Organization. Treatment of drug-resistant tuberculosis. Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010. p. 83–94.

21. Olaru ID, Lange C, Indra A, Meidlinger L, Huhulescu S, Rumetshofer R. High Rates of Treatment Success in Pulmonary Multidrug-Resistant Tuberculosis by Individually Tailored Treatment Regimens. Ann Am Thorac Soc. 2016;13(8):1271–8.

22. Jain K, Desai M, Solanki R, Dikshit RK. Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis. J Pharmacol Pharmacother. Medknow Publications and Media Pvt. Ltd.; 2014;5(2):145–9.

23. Ramachandran G, Swaminathan S. Safety and Tolerability Profile of Second-Line Anti-Tuberculosis Medications. Drug Saf. 2015;38(3):253–69.

24. Laurenzi M, Ginsberg A, Spigelman M. Challenges Associated with Current and Future TB Treatment. Infect Disord - Drug Targets. 2007;7:105–19.

25. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, et al. Outcomes of Multi-Drug Resistant Tuberculosis (MDR-TB) among a Cohort of South African Patients with High HIV Prevalence. PLoS One. 2011;6(7).

26. Malangu N, Ibrahim MO. Tuberculosis treatment outcomes in patients with resistant tuberculosis at a district hospital in Kwazulu-Natal Province of South Africa. Botswana J African Stud. 2014;28(1):51–62.

27. Sloan DJ, Lewis JM. Management of multidrug-resistant TB: novel treatments and their expansion to low resource settings. Trans R Soc Trop Med Hyg. Oxford University Press; 2016;110(3):163–72.

28. Andrews JR, Shah NS, Gandhi N, Moll T, Friedland G, Tugela Ferry Care and Research (TF CARES) Collaboration. Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. J Infect Dis. Oxford University Press; 2007;(Supplement 3):S482-90.

29. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. Int J Tuberc lung Dis. 2010;14(3):275–81.

30. Problems of multidrug- and extensively drug-resistant TB. Drug Ther Bull. 2012;50(2):21–4.

31. Venkatesh KK, Swaminathan S, Andrews JR, Mayer KH. Tuberculosis and HIV co-infection: screening and treatment strategies. Drugs. 2011;71(9):1133–52.

32. Zumla A, Malon P, Henderson J, Grange JM. Impact of HIV infection on tuberculosis. Postgrad Med J. 2000;76(895):259–68.

33. van der Walt M, Lancaster J, Odendaal R, Davis JG, Shean K, Farley J. Serious treatment related adverse drug reactions amongst anti-retroviral naïve MDR-TB patients. PLoS One. 2013;8(4):e58817.

34. Schnippel K, Berhanu RH, Black A, Firnhaber C, Maitisa N, Evans D, et al. Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. BMC Infect Dis. BioMed Central; 2016;16(1):593.

35. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J, Saranchuk P, et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLoS One. 2012;7(7):e40781.

Chapter 4

36. Wilkins JJ, Langdon G, Mcilleron H, Pillai G, Smith PJ, Simonsson USH. Variability in the population pharmacokinetics of isoniazid in South African tuberculosis patients. Br J Clin Pharmacol. 2011;72(1):51–62.

37. Masimirembwa C, Hasler J a. Pharmacogenetics in Africa, an Opportunity for Appropriate Drug Dosage Regimens: on the Road to Personalized Healthcare. Pharmacometrics Syst Pharmacol. 2013;2(5):e45.

38. Chaudhry M, Alessandrini M, Pepper MS. Pharmacogenomics for infectious diseases in sub-Saharan Africa: Successes and opportunities. Appl Transl Genomics. 2016;9:3–5.

39. Tabuti JRS, Kukunda CB, Waako PJ. Medicinal plants used by traditional medicine practitioners in the treatment of tuberculosis and related ailments in Uganda. J Ethnopharmacol. 2010;127(1):130–6.

40. Orodho JA, Kirimuhuzya C, Otieno JN, Magadula JJ, Okemo P. Local Management of Tuberculosis by Traditional Medicine Practitioners in Lake Victoria Region. Open Complement Med J. 2011;3(1):1–9.

41. Semenya SS, Maroyi A. Medicinal plants used for the treatment of tuberculosis by Bapedi traditional healers in three districts of the Limpopo Province, South Africa. African J Tradit Complement Altern Med. 2013;10(2):316–23.

42. European Centre for Disease Prevention and Control (ECDC). Healthcare system factors influencing treatment results of patients with multidrug-resistant tuberculosis. Stockholm; 2014.

43. Ministry of Health and Social Services (MoHSS). National Guidelines for the Management of Tuberculosis. 3rd ed. Windhoek: MoHSS; 2012.

44. Mkopi A, Range N, Lwilla F, Egwaga S, Schulze A, Geubbels E, et al. Adherence to Tuberculosis Therapy among Patients Receiving Home-Based Directly Observed Treatment: Evidence from the United Republic of Tanzania. PLoS One. 2012;7(12):1–7.

45. Avong YK, Isaakidis P, Hinderaker SG, Van den Bergh R, Ali E, Obembe BO, et al. Doing No Harm? Adverse Events in a Nation-Wide Cohort of Patients with Multidrug-Resistant Tuberculosis in Nigeria. PLoS One. 2015;10(3):e0120161.

46. Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K. "I cry every day": experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. Trop Med Int Heal. 2013 Sep;18(9):1128–33.

47. Sotgiu G, D'Ambrosio L, Centis R, Mura I, Castiglia P, Spanevello A, et al. The multidrug-resistant tuberculosis threat: old problems and new solutions. J Thorac Dis. AME Publications; 2015;7(9):E354-60.

48. Gebremariam MK, Bjune GA, Frich JC. Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study. BMC Public Health. 2010;10:651.

49. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis-2011 update. 2011th ed. Geneva: WHO; 2011.

50. Modongo C, Sobota RS, Kesenogile B, Ncube R, Sirugo G, Williams SM, et al. Successful MDR-TB treatment regimens including Amikacin are associated with high rates of hearing loss. BMC Infect Dis. 2014;14(1):542.

51. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis. 2004;38(11):1538–44.

52. Li J, Burzynski JN, Lee Y-A, Berg D, Driver CR, Ridzon R, et al. Use of Therapeutic Drug Monitoring for Multidrug-Resistant Tuberculosis Patients. Chest. 2004;126(6):1770–6.

53. de Jager P, Altena R Van. Hearing loss and nephrotoxicity in long-term aminoglycoside. Int J Tuberc Lung Dis. 2002;6(7):622–7.

54. van Altena R, Dijkstra JA, van der Meer ME, Borjas Howard JF, Kosterink JGW, van Soolingen D, et al. Reduced chance of hearing loss associated with Therapeutic Drug Monitoring of aminoglycosides in the treatment of Multidrug Resistant Tuberculosis. Antimicrob Agents Chemother. American Society for Microbiology; 2017;61(1):doi:10.1128/AAC.01400-16.

55. Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol. 2012;73(1):27–36.

56. Heysell SK, Moore JL, Peloquin CA, Ashkin D, Houpt ER. Outcomes and use of therapeutic drug monitoring in multidrug-resistant tuberculosis patients treated in virginia, 2009-2014. Tuberc Respir Dis (Seoul). 2015;78(2):78–84.

57. Alffenaar J-WC, Tiberi S, Verbeeck RK, Heysell SK, Grobusch MP. Therapeutic Drug Monitoring in Tuberculosis: Practical Application for Physicians. Clin Infect Dis. 2017;64(1):104–5.

58. Balakrishnan I, Shorten RJ. Therapeutic drug monitoring of antimicrobials. Ann Clin Biochem. 2016;53(3):333–46.

59. Melnick JZ, Baum M, Thompson JR. Aminoglycoside-induced Fanconi's syndrome. Am J kidney Dis. 1994;23(1):118–22.

60. Verdel BM, van Puijenbroek EP, Souverein PC, Leufkens HGM, Egberts ACG. Drug-related nephrotoxic and ototoxic reactions : a link through a predictive mechanistic commonality. Drug Saf. 2008;31(10):877–84.

61. Ambrosio LD, Centis R, Sotgiu G, Pontali E, Spanevello A, Migliori GB. New anti-tuberculosis drugs and regimens : 2015 update. Eur Respir J. 2015;1.

62. Zumla AI, Gillespie SH, Hoelscher M, Philips PPJ, Cole ST, Abubakar I, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. Lancet Infect Dis. Elsevier Ltd; 2012;14(4):327–40.

63. Brigden G, Hewison C, Varaine F. New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid. Infect Drug Resist. 2015;8:367–78.

64. Stop TB Partnership. Global Drug Facility. Geneva: WHO; 2009.

65. Kakayeva S, Salakaia A. Strengthening the TB pharmaceutical management system and ensuring patients' uninterrupted access to anti-TB medicines in Uzbekistan. Arlington, Virginia; 2015.

66. Lessem E, Cox H, Daniels C, Furin J, McKenna L, Mitnick CD, et al. Access to new medications for the treatment of drug-resistant tuberculosis: Patient, provider and community perspectives. Int J Infect Dis. International Society for Infectious Diseases; 2015;32:56–60.

67. Kazi AN, Mohiuddin H. Pakistan is hit by a shortage of anti-tuberculosis drugs. BMJ. 2016;353.

68. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet. Elsevier Ltd; 2009;373(9659):240–9.

69. Lunte K, Cordier-lassalle T, Keravec J. Lessons from the Reducing the price of treatment for multidrug-resistant tuberculosis through the Global Drug Facility. Bull World Health Organ. 2015;93:279–82.

Chapter 4

70. Tupasi TE, Gupta R, Quelapio MID, Orillaza RB, Mira NR, Mangubat N V, et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006;3(9):e352.

71. Hwang TJ, Keshavjee S. Global Financing and Long-Term Technical Assistance for Multidrug-Resistant Tuberculosis : Scaling Up Access to Treatment. PLoS Med. 2014;11(9).

72. Medecins Sans Frontieres. Access: Developing countries hit with high price for important new tuberculosis drug [Internet]. 2016 [cited 2017 Feb 8]. Available from: http://www.msf.org/en/article/access-developing-countries-hit-high-price-important-new-tuberculosis-drug

73. Achoki T, Lesego A. Implementing Health Financing Reforms in Africa : Perspectives of Health System Stewards. Ann Glob Heal. 2016;October.

74. Long Q, Qu Y, Lucas H. Drug-resistant tuberculosis control in China: progress and challenges. Infect Dis Poverty. 2016;5(1):9.

75. Ruan YZ, Li RZ, Wang XX, Wang LX, Sun Q, Chen C, et al. The affordability for patients of a new universal MDR-TB coverage model in China. Int J Tuberc Lung Dis. 2016;20(5):638–44.

76. World Health Organization (WHO). The End TB Strategy. Geneva: WHO; 2015.

77. World Health Organization (WHO). Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO; 2010.

78. World Health Organization (WHO). A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: Enhancing the safety of the TB patient. Geneva: World Health Organization; 2012.

79. World Health Organization. Management of adverse effects and pharmacovigilance. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014.

80. World Health Organization (WHO). Active tuberculosis drug-safety monitoring and management. Geneva; 2015.

81. Sotgiu G, Alffenaar J-WC, Centis R, D'Ambrosio L, Spanevello A, Piana A, et al. Therapeutic drug monitoring: how to improve drug dosage and patient safety in tuberculosis treatment. Int J Infect Dis. International Society for Infectious Diseases; 2015;32:101–4.

82. Verbeeck RK, Günther G, Kibuule D, Hunter C, Rennie TW. Optimizing treatment outcome of first-line anti-tuberculosis drugs: the role of therapeutic drug monitoring. Eur J Clin Pharmacol. 2016;72(8):905–16.

83. Ma Q, Lu AYH. Pharmacogenetics, Pharmacogenomics, and Individualized Medicine. Pharmacol Rev. 2011;63(2):437–459.

84. Bolhuis MS, Alffenaar JWC, Akkerman OW, De Lange WCM, Van Der Werf TS, Sturkenboom MGG. Individualized treatment of multidrug-resistant tuberculosis using therapeutic drug monitoring. Int J Mycobacteriology. 2016;5(419):S44–5.

85. Olaru ID, Lange C, Heyckendorf J. Personalized medicine for patients with MDR-TB. J Antimicrob Chemother. 2016;71(4):852–5.

86. Phelan J, O'Sullivan DM, Machado D, Ramos J, Whale AS, O'Grady J, et al. The variability and reproducibility of whole genome sequencing technology for detecting resistance to anti-tuberculous drugs. Genome Med. Genome Medicine; 2016;8(1):132.

87. Perletti G, Vral A, Patrosso MC, Marras E, Ceriani I, Willems P, et al. Prevention and modulation of aminoglycoside ototoxicity (Review). Mol Med Rep. 2008;1(1):3–13.

88. Xie J, Talaska AE, Schacht J. New developments in aminoglycoside therapy and ototoxicity. Hear Res. 2011;28(1–2):28–37.

89. Mandel W. Pyridoxine and the Isoniazid-Induced Neuropathy. Chest. 1959;36(3):293–6.

90. Tepel M. N-Acetylcysteine in the prevention of ototoxicity. Kidney Int. Elsevier Masson SAS; 2007;72(3):231–2.

91. Rybak LP, Mukherjea D, Jajoo S, Ramkumar V. Cisplatin Ototoxicity and Protection: Clinical and Experimental Studies. Tohoku J Exp Med. 2009;219(3):177–86.

92. Li J, Woo CW. Finding ways to solve or prevent aminoglycoside-induced ototoxicity? Ann Transl Med. 2016;4(24):533–533.

93. Moodley R, Godec TR. Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials. Eur Respir Rev. 2016;25(139):29–35.

94. Kumar BA. Rehabilitation of treated TB patients: Social, psychological and economic aspects. Heal Act Public Heal Consult. 2016;5:S129–30.

95. Systems for Improved Access to Pharmaceuticals and Services (SIAPS). Drug Use Reviews—A Practical Strategy to Ensure the Appropriate Use of Anti-Tuberculosis Medicines. Arlington, Virginia: Management Sciences for Health (MSH); 2014.

96. The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide. Second. Boston, USA; 2015.

97. Mckenna L. The Pediatric Tuberculosis Treatment Pipeline : Beyond Pharmacokinetics and Safety Data. 2016.

98. Shah I. Multidrug-resistant tuberculosis in children and response to therapy. Med J Dr DY Patil Univ. 2015;8(2):199.

99. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Perez-Velez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: Systematic review and global estimates. Lancet. 2014;383(9928):1572–9.

100. Simon Schaaf H. Update on multidrug-resistant tuberculosis in children. Int J Mycobacteriology. 2016;5:S7.

101. Medecins Sans Frontiers (MSF) | Doctors without borders. No more injections! [Internet]. Online Blog. 2011 [cited 2017 Feb 11]. Available from: http://blogs.msf.org/en/patients/blogs/tb-me/no-more-injections

102. Furin J, Mafukidze A, Brigden G, Du Cros P, Golin R, Harausz E, et al. A bitter pill to swallow: The need for better medications for drug-resistant tuberculosis in children. Int J Tuberc Lung Dis. 2015;19(12):S55–60.

103. Schaaf HS, Thee S, van der Laan L, Hesseling AC, Garcia-Prats AJ. Adverse effects of oral second-line antituberculosis drugs in children. Expert Opin Drug Saf. 2016;15(10):1369–81.

104. Garcia-Prats AJ, Schaaf HS, Hesseling AC. The safety and tolerability of the second-line injectable antituberculosis drugs in children. Expert Opin Drug Saf. 2016;15(11):1491–500.

105. Hallbauer UM, Schaaf HS. Ethionamide-induced hypothyroidism in children. South Afr J Epidemiol Infect. 2011;26(3):161–3.

106. Seddon JA, Thee S, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS, et al. Hearing loss in children treated for multidrug-resistant tuberculosis. J Infect. 2013;66(4):320–9.

107. Franck C, Seddon JA, Hesseling AC, Schaaf HS, Skinner D, Reynolds L. Assessing the impact of multidrug-resistant tuberculosis in children: an exploratory qualitative study. BMC Infect Dis. 2014;14:426.

108. Laventhal N, Tarini B, Lantos J. Ethical Issues in Neonatal and Pediatric Clinical Trials. Pediatr Clin North Am. 2012;59(5):1205–1220.

109. Schaaf H, Garcia-Prats A, Donald P. Antituberculosis drugs in children. Clin Pharmacol Ther. 2015 Sep;98(3):252–65.

Chapter 4

110. Taneja R, Furin J, Maheshwari HK. Paediatric formulations of second-line anti-tuberculosis medications: challenges and considerations. Int J Tuberc Lung Dis. 2015;19(12):61–9.

111. Ankrah DNA, Turkson JT, Boateng EB, Amegavie FTT, Bruce E. Insufficient access to oral paediatric medicines in Ghana: A descriptive study. BMC Health Serv Res. 2016;16(1):198.

112. Ivanovska V, Rademaker CM a, van Dijk L, Mantel-Teeuwisse AK. Pediatric Drug Formulations: A Review of Challenges and Progress. Pediatrics. 2014;134(2):361–72.

113. Piñeiro Pérez R, Santiago García B, Fernández-Llamazares CM, Baquero Artigao F, Noguera Julian A, Mellado Peña MJ. The challenge of administering anti-tuberculosis treatment in infants and pre-school children. pTBred Magistral Project. An Pediatría (English Ed. Elsevier; 2016 Jul;85(1):4–12.

114. Esposito S. Living with the challenges of treating tuberculosis. Breathe. 2015;11(1).

115. Furin J, Brigden G, Lessem E, Becerra MC. Novel pediatric delivery systems for second-line anti-tuberculosis medications: A case study. Int J Tuberc Lung Dis. 2013;17(9):1239–41.

116. Thee S, Garcia-Prats AJ, McIlleron HM, Wiesner L, Castel S, Norman J, et al. Pharmacokinetics of ofloxacin and levofloxacin for prevention and treatment of multidrug-resistant tuberculosis in children. Antimicrob Agents Chemother. 2014;58(5):2948–51.

117. Achar J, Berry C, Herboczek K, Parpieva N, Tillyashaykhov MN, Tigay ZN, et al. Multidrug-resistant tuberculosis in child successfully treated with 9-month drug regimen. Emerg Infect Dis. 2015;21(11):2105–6.

118. TB Alliance. Child-friendly medicines [Internet]. [cited 2017 Jan 23]. Available from: https://www.tballiance.org/child-friendly-medicines

119. Malhotra S, Ursu I, Ghoneim R, Paredes Jodrey P, Soucy Brown M, Barr-Dichiara M. From availability to uptake: Planning for the introduction of new, child-friendly anti-tuberculosis formulations. Int J Tuberc Lung Dis. 2015;19(12):S32–8.

120. Seddon JA, Schaaf SH. Drug-resistant tuberculosis and advances in the treatment of childhood tuberculosis. Pneumonia. Pneumonia; 2016;6(2):314–20.

121. Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G, et al. Towards early inclusion of children in tuberculosis drugs trials: A consensus statement. Lancet Infect Dis. Elsevier Ltd; 2015;15(6):711–20.

122. Treatment Action Group. TB Drugs for Children [Internet]. [cited 2017 Jan 23]. Available from: http://www.treatmentactiongroup.org/tagline/2013/spring/tb-drugs-children

123. Reichman LB. TIMEBOMB revisited 10 years later: can we sustain progress or are we losing the war? Int J Tuberc Lung Dis. 2013;17(11):1377–82.

124. Martin J, Shenfield G. The hazards of rapid approval of new drugs. Aust Prescr. 2016;39(1):2–3.

125. Lexchin J. New Drugs and Safety: What Happened to New Active Substances Approved in Canada Between 1995 and 2010. Arch Intern Med. 2012;172(21):1680–1.

126. Wren K. Faster Approval of New Medical Products Heightens Uncertainty Over Risks | AAAS [Internet]. 2014 [cited 2017 Mar 21]. Available from: https://www.aaas.org/news/faster-approval-new-medical-products-heightens-uncertainty-over-risks

127. Owunna C, Yedilbayev A. The 46th Union World Conference on Lung Health. Pharmacovigilance for bedaquiline, delamanid and other TB drugs and regimens. Cape Town, South Africa: The Union; 2015.

128. Sullivan T, Ben Amor Y. Global Introduction of New Multidrug-Resistant Tuberculosis Drugs—Balancing Regulation with Urgent Patient Needs. Emerg Infect Dis. 2016;22(3).

129. Sreekanth AS. A Pharmacovigilance Study on Antitubercular Therapy in the Department of Pulmonary Medicine at a Tertiary Care Hospital. IOSR J Dent Med Sci. 2015;14(8):2279–861.

130. Soussi Tanani D, Tebaa A, Benkirane R, Bennani K, Iraqi G, Soulaymani A, et al. Pharmacovigilance and moroccan tuberculosis public program: current situation. Tuberc Res Treat. 2014;2014:626797.

131. Isah AO, Pal SN, Olsson S, Dodoo A, Bencheikh RS. Specific features of medicines safety and pharmacovigilance in Africa. Ther Adv Drug Saf. 2012;3(1):25–34.

132. Xueref S, Daviaud J, Pal S, S. X, J. D, S. P. The Global Fund and pharmacovigilance systems in resourcelimited settings. Lancet. 2013;381(9875):1360.

133. Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. Expert Rev Clin Pharmacol. 2015;8(4):449–60.

134. Strengthening Pharmaceutical Systems (SPS) Program, USAID. Supporting Pharmacovigilance in Developing Countries: The Systems Perspective. Arlington, Virginia: Management Sciences for Health (MSH); 2009.

135. Katz MG, Kripalani S, Weiss BD. Use of pictorial aids in medication instructions: A review of the literature. Am J Heal Pharm. 2006;63(23):2391–7.

136. Del Re L, Vaillancourt R, Villarreal G, Pouliot A. Pictograms: Can They Help Patients Recall Medication Safety Instructions? Visible Lang. 2016;50(1):127.

137. Lu Z. Information technology in pharmacovigilance: Benefits, challenges, and future directions from industry perspectives. Drug Healthc Patient Saf. 2009;1(1):35–45.

138. Persaud-Sharma V, Zhou S-F. Incorporation of New Technologies into Global Pharmacovigilance. J Pharmacovigil. 2013;1(1):1–5.

139. Koutkias VG, Jaulent MC. Computational Approaches for Pharmacovigilance Signal Detection: Toward Integrated and Semantically-Enriched Frameworks. Drug Saf. 2015;38(3):219–32.

140. World Health Organization (WHO). The Safety of Medicines in Public health programmes: Pharmacovigilance an essential tool. Geneva: WHO; 2006.

141. Pal SN, Olsson S, Brown EG. The monitoring medicines project: a multinational pharmacovigilance and public health project. Drug Saf. 2015;38(4):319–28.

142. Toklu HZ, Mensah E. Why do we need pharmacists in pharmacovigilance systems? Online J Public Health Inform. 2016;8(2):e193.

143. Kumar A. Pharmacovigilance: Importance, concepts, and processes. Am J Heal Syst Pharm. 2017;74(1):101–7.

144. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: Complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75–81.

145. Skrahina A, Hurevich H, Falzon D, Zhylevich L, Rusovich V, Dara M, et al. Active pharmacovigilance for multidrug-resistant tuberculosis patients treated with Linezolid, Belarus – 2014-2015. Eur Respir J. 2015;46(suppl 59).

146. Mann M, Mengistu A, Gaeseb J, Sagwa E, Mazibuko G, Babigumira JB, et al. Active Surveillance versus Spontaneous Reporting for First-Line Antiretroviral Medicines in Namibia: A Cost–Utility Analysis. Drug Saf. 2016;39(9):859–72.

147. Mehta U, Dheda M, Steel G, Blockman M, Ntilivamunda A, Maartens G, et al. Strengthening pharmacovigilance in South Africa. South African Med J. 2014;104(2):104–6.

Chapter 4

148. Systems for Improved Access to Pharmaceuticals and Services (SIAPS). Development of Active Surveillance System for the Antiretroviral Program in Karnataka State — Protocol and Operational Plan. Arlington, Virginia: Management Sciences for Health (MSH); 2011.

149. Mann M, Mengistu A, Gaeseb J, Sagwa E, Mazibuko G, Baeten JM, et al. Sentinel site active surveillance of safety of first-line antiretroviral medicines in Namibia. Pharmacoepidemiol Drug Saf. 2016;25(9):1052–60.

150. Corbell C, Katjitae I, Mengistu A, Kalemeera F, Sagwa E, Mabirizi D, et al. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. Pharmacoepidemiol Drug Saf. 2012;21(4):407–14.

151. Desai S. Technology Unlocking the Potential of Social Media in Drug Safety. J Clin Stud. 2015;7(3).

152. Sarker A, Ginn R, Nikfarjam A, O'Connor K, Smith K, Jayaraman S, et al. Utilizing social media data for pharmacovigilance: A review. J Biomed Inform. 2015;54:202–12.

153. Sarker A, O'Connor K, Ginn R, Scotch M, Smith K, Malone D, et al. Social Media Mining for Toxicovigilance: Automatic Monitoring of Prescription Medication Abuse from Twitter. Drug Saf. 2016;39(3):1–10.

154. Ministry of Health and Social Services (MoHSS). National Tuberculosis and Leprosy Programme Annual Report: 2015-2016. Windhoek; 2016.

155. Kajungu DK, Erhart A, Talisuna AO, Bassat Q, Karema C, Nabasumba C, et al. Paediatric pharmacovigilance: Use of pharmacovigilance data mining algorithms for signal detection in a safety dataset of a paediatric clinical study conducted in seven African countries. PLoS One. 2014;9(5).

156. Rachlis B, Karwa R, Chema C, Pastakia S, Olsson S, Wools-Kaloustian K, et al. Targeted Spontaneous Reporting: Assessing Opportunities to Conduct Routine Pharmacovigilance for Antiretroviral Treatment on an International Scale. Drug Saf. Springer International Publishing; 2016;39(10):959–76.

157. Cline GB, Luiz JM. Information technology systems in public sector health facilities in developing countries: the case of South Africa. BMC Med Inform Decis Mak. 2013;13(1):13.

158. Akanbi MO, Ocheke AN, Agaba PA, Daniyam CA, Agaba EI, Okeke EN, et al. Use of Electronic Health Records in sub-Saharan Africa: Progress and challenges. J Med Trop. 2012;14(1):1–6.

159. Mutale W, Chintu N, Amoroso C, Awoonor-Williams K, Phillips J, Baynes C, et al. Improving health information systems for decision making across five sub-Saharan African countries: Implementation strategies from the African Health Initiative. BMC Heal Serv Res. 2013;13 Suppl 2(Suppl 2):S9.

160. Ohuabunwa EC, Sun J, Jean Jubanyik K, Wallis LA. Electronic Medical Records in low to middle income countries: The case of Khayelitsha Hospital, South Africa. African J Emerg Med. African Federation for Emergency Medicine; 2016;6(1):38–43.

161. Tierney WM, Achieng M, Baker E, Bell A, Biondich P, Braitstein P, et al. Experience implementing electronic health records in three East African countries. Stud Health Technol Inform. 2010;160(PART 1):371–5.

162. Coleman A. An Integrated Model to Share Patient Health Records in Public and Private Hospitals in South Africa. 2013;7(2):87–93.

Summary

Samenvatting

SUMMARY

Tuberculosis (TB) is an ancient, deadly disease that is steadily creeping back to afflict the world today. More disconcerting though, is the unprecedented emergence and spread of drug-resistant strains of *Mycobacterium tuberculosis*, which have been observed in several countries including sub-Saharan Africa and other parts of the world. Multidrug-resistant tuberculosis (MDR-TB), along with other extreme forms of resistance of *M. tuberculosis*, is a growing global menace that is seriously undermining the previous successes made in the control and elimination of TB. In 2015 alone, there were an estimated 480,000 new cases of MDR-TB, globally, as reported by the World Health Organization. The majority of these cases were from India, China and the Russian Federation. Unfortunately, the main cause of drug resistance of *M. tuberculosis* is the improper use of current anti-TB drugs. Overall, the global MDR-TB treatment success rates have been unsatisfactory, at around 52%. Yet MDR-TB is treatable using second-line anti-TB drugs, if taken correctly and completely. However, the safety and tolerability of current second-line anti-TB drugs has remained a key concern for the successful treatment of MDR-TB, because of the frequent occurrence of adverse events.

The treatment of MDR-TB takes a long time, is complex, and is frequently associated with the occurrence of a range of adverse drug reactions. Some of these adverse drug reactions, such as ototoxicity, nephrotoxicity and hepatotoxicity, could severely diminish a person's health-related quality of life (HRQoL). The occurrence of severe or serious treatment-related adverse events, along with other disease-related sequelae, may impair patients' ability to perform activities of daily life during or after MDR-TB treatment. In Namibia, the rate of MDR-TB infection continues to be high, although it has been declining over the years. The high Human Immunodeficiency Virus (HIV) co-infection rate in the country has posed a unique challenge for concomitantly treating TB and HIV infection.

This thesis aimed at investigating the real-world safety of second-line anti-TB medicines in the context of the national MDR-TB treatment program in Namibia. The research was conducted under three objectives: (i) to determine the occurrence, risk factors and clinical management of adverse events associated with MDR-TB treatment; (ii) examine the epidemiology of serious adverse events of aminoglycosides in the presence or absence of HIV infection - with or without antiretroviral therapy (ART); and (iii) assess the link between the occurrence of adverse events and patients' perception of their health-related quality of life (HRQoL), at the end of MDR-TB treatment.

The thesis is organized into four main chapters. **Chapter 1** is introductory and provides a general overview of the research topic, the aim and the objectives of the research. The subsequent chapters are summarized below.

Notably, safety remains a key concern of the current (old) medicines for treating MDR-TB. Indeed, **Chapter 2.1** aimed to assess the prevalence, profile and outcome of adverse events (AEs) that are associated with the treatment of MDR-TB and to explore possible influences of HIV infection on the occurrence of adverse events. This was a cross-sectional descriptive study using retrospective data collected from treatment records of all the 59 patients treated for DR-TB at a 25-bed MDR-TB treatment ward in Namibia from January 2008 to February 2010, using a structured data collection form. A total of 141 adverse events of varying severity were experienced in 90% (53/59) of patients. The TB/HIV co-infection rate was 53% (n=31). The prevalence of gastrointestinal tract adverse events was 64%, tinnitus 45%, joint pain 28% and decreased hearing 25%. These adverse events were of varying severity and were predominant during the intensive phase of MDR-TB treatment. While most of the patients were able to tolerate the adverse events, about 10% experienced serious adverse events that were potentially debilitating. Moreover, some adverse events such as abdominal pains, rash, nausea, decreased hearing, and joint pain were overlapping and were more prevalent among the MDR-TB patients co-infected with HIV than in the uninfected patients. Therefore, clinicians should closely monitor and aggressively manage adverse events during the intensive phase of MDR-TB treatment and should always consider the possibility of increased occurrence of adverse events in patients co-infected with HIV.

Consequently in **Chapter 2.2**, we compared the occurrence of adverse events among patients undergoing concomitant MDR-TB and HIV treatment, with those who were treated for MDR-TB infection alone. The main objective of this study was to compare the absolute risks and risk factors for commonly observed adverse events (occurring in at least 20% of patients) during MDR-TB treatment in HIV-infected and HIV-uninfected patients. This was a retrospective cohort analysis of patients treated for MDR-TB between January 2008 and February 2010 at the Kondja MDR-TB ward in Namibia. Data were anonymously collected from patients' treatment records using a structured form, and then analyzed using descriptive statistics and 2 x 2 contingency tables, stratified by HIV status. There were 57 patients included in the analysis, 31 (53%) of whom were co-infected with HIV. Of the 18 routinely monitored adverse events, tinnitus (40%), joint pain (26%), hearing loss (23%) and nausea (21%) were the most common. Only abdominal pain had a statistically significant difference in the risk of occurrence among HIV infected patients compared with HIV uninfected patients (26% vs 4%, p = 0.02). Generally, adverse event occurrence and the associated risk factors were similar between the comorbid MDR-TB/HIV patients compared with the MDR-TB only patients. In some instances, the presence of HIV infection appeared to modify the effects of the risk factors on the occurrence of tinnitus, joint pain, hearing loss, and nausea. However, these findings were considered inconclusive because of the low statistical power of

the study. A prospective study with a larger sample size to increase the power and the confidence in the results was recommended.

Further, **Chapter 2.3** set out to determine the incidence of symptomatic moderate-to-severe adverse events during treatment of MDR-TB, and to compare their risk and outcomes by patients' HIV co-infection status using the same cohort as in **Chapter 2.2**. Over the course of MDR-TB treatment, clinicians monitored and managed patients' response to treatment until its completion. Any symptomatic adverse event that was observed by the clinician or reported by the patient was recorded in the patient's MDR-TB treatment booklet. There were 18 symptomatic adverse events routinely monitored. Depending on the nature of the intervention needed, each was graded as mild, moderate or severe. Data were extracted from the patient treatment booklet using a structured form, then descriptive, bivariate and Cox proportional hazard analysis were performed, stratified by patients' HIV infection status. Fifty seven patients with MDR-TB were identified, 31 (53%) of whom were HIV co-infected. The cumulative incidence of moderate-to-severe adverse events was 46 events in 100 patients. HIV co-infected patients experienced more moderate-to-severe adverse events compared with the HIV uninfected patients (median 3 versus 1 events, p=0.01). They had a four-fold increase in the cumulative hazard of moderate-to-severe adverse events compared with the HIV uninfected patients (HR=4.0, 95% CI 1.5 – 10.5). Moderate-to-severe adverse events were the main determinant of a clinician's decision to reduce the dose or to stop the suspected offending medicine (RR=3.8, 95% 1.2-11.8). Clinicians should, therefore, employ various strategies for preventing drug-induced patient discomfort and harm, such as reducing the dose or stopping the suspected offending medicine, during MDR-TB treatment. Managers of tuberculosis control programmes should strengthen pharmacovigilance systems. In addition, we recommend a more powered study for conclusive risk-factor analysis.

Does the occurrence of adverse events influence patients' perception of their health-related quality of life at the end of MDR-TB treatment? We explored this question in **Chapter 2.4**, in which a cross-sectional analytic survey of patients completing or who recently completed MDR-TB treatment was conducted. The patients rated their HRQoL using the simplified Short Form-™ (SF-8) questionnaire consisting of eight Likert-type questions (four questions each for the physical and mental health components, respectively). Three supplemental questions on the treatment-associated adverse events that the patients may have experienced were also included. The scoring of patient's HRQoL ratings was norm-based (mean=50, standard deviation =10) ranging from 20 (worst health) to 80 (best health), rather than the conventional 0-100 scores. The internal consistency of the scale items was assessed using Cronbach's alpha. Descriptive analyses were used to summarize the scores, and associations between the patients' HRQoL scores and adverse events were evaluated using bivariate methods. Overall,

36 patients (20 males, 56%) aged 17-54 years (median=40 years) responded to the questionnaire. The study found that patients who completed their MDR-TB treatment in Namibia tended to score moderately low on their HRQoL, using the generic SF-8™ questionnaire. Indeed, the median (range) HRQoL score for the physical component summary was 58.6 (35.3-60.5), while the median score for the mental component summary was 59.3 (26.6-61.9), indicating not-so-high self-rating of health. The occurrence of adverse events was not related to HRQoL scores. For patients reporting zero to two events, the median (range) HRQoL score was 56.8 (44.4-56.8), while for those reporting three or more events, the median score was 55.2 (38.6-56.8); p=0.34 for difference between these scores. Thus, there was no association between the patients' HRQoL scores upon treatment completion and the occurrence of adverse events. This implies that MDR-TB disease itself may be associated with a decrement of HRQoL, rather than the occurrence of adverse events. This finding needs to be confirmed in a larger study that measures HRQoL at baseline, at multiple time points during the MDR-TB treatment phases and at the completion of treatment so that the changes in HRQoL may be ascertained.

To date, amikacin, kanamycin and capreomycin are still an essential component of the intensive phase of MDR-TB treatment. Unfortunately, these injectable drugs are stubbornly associated with a significant risk of hearing loss and/or renal insufficiency. The ototoxicity of aminoglycosides and capreomycin was the subject of the research presented in **Chapter 3.1**. The aim of this study was to evaluate the association between the use of streptomycin, amikacin, kanamycin and capreomycin in TB treatment and the global pharmacovigilance reporting of ototoxicity (deafness or hearing loss, tinnitus and vertigo). Second, the study aimed to analyze patient demographic and geographic factors that influence the reporting of ototoxicity in TB treatment. A case/non-case disproportionality analysis of the VigiBase® individual case safety reports (ICSRs) of patients treated for TB using multidrug regimens that contain either of streptomycin, amikacin, kanamycin or capreomycin was conducted. Cases were reports of ototoxicity; non-cases were other adverse drug reactions (ADRs). The unit of analysis was the drug-ADR pair. We calculated reporting odds ratios (RORs) and their 95% confidence intervals (CI). The referent drug was streptomycin. By June 2014, there were 3361 drug-ADR pairs in VigiBase® (1693 ICSRs) where the parenteral administration of the four drugs for TB treatment was suspected of causing the reported ADRs. Deafness, tinnitus and vertigo were reported in 576 drug-ADR pairs (cases), the rest being other ADRs (non-cases). We found that the reporting of deafness in VigiBase® in the context of tuberculosis treatment was most disproportionately associated with amikacin use (ROR 9.3; 95%CI 3.8-23.0), followed by kanamycin use (ROR 4.3; 95%CI 1.3-14.2). On the other hand, the reporting of vertigo was inversely associated with capreomycin use (ROR 0.1; 95%CI 0.01-0.4). Patient age and sex had no influence on the reporting

of cases of deafness that were suspected to be caused by the use of aminoglycoside or capreomycin for TB treatment, in VigiBase®. However, there was a noticeable geographic difference in the reporting of ototoxicity. Compared to Africa, there was a disproportionately higher reporting of ototoxicity by the Americas (ROR 4.0; 95%CI 1.7–9.3), Asia (ROR 5.1; 95%CI 2.4–11.0) and Europe (ROR 4.8; 95%CI 2.2–10.4). Deafness or tinnitus was the predominant type of ototoxicity reported from the Americas (ROR 5.0; 95%CI 1.4–17.3), while vertigo was mostly reported by countries in Asia (ROR 6.6; 95%CI 2.4–17.9). Europe had almost similar reporting of deafness/tinnitus (ROR 3.8; 95%CI 1.2–12.4) and vertigo (ROR 4.6; 95%CI 1.7–12.6). This could be a reflection of the global TB epidemiology; as well as the extent of development and the level of functionality of pharmacovigilance systems of the countries participating in the WHO global programme for monitoring the safety of medicines.

Amikacin and kanamycin, which continue to be the mainstay of MDR-TB treatment, especially in developing countries where the burden of MDR-TB is highest, may cause dose-dependent irreversible hearing loss, if not properly used. In view of this, **Chapter 3.2** compared the cumulative incidence of hearing loss among patients treated for MDR-TB with amikacin or kanamycin-based regimens, and also sought to identify the most-at-risk patients, based on real-life clinical experiences in a Namibian retrospective cohort (N=353). Data were obtained for patients who were treated and audiologically assessed as part of their clinical care during MDR-TB treatment, for the period between June 2004 and March 2014. The study outcome was the occurrence of any hearing loss. Proportions were compared using the Chi-square test, while stratified analysis and logistic regression were applied to study the risk of hearing loss; and to identify the most-at-risk patients through effect-modification.

All the 353 patients had normal baseline hearing, while 46 % were HIV co-infected. The cumulative incidence of all forms of hearing loss was 58 %. In terms of severity, some were moderate (23%), moderate-severe (16%), severe (10%), or profound (15%), while the rest were mild (32%). The long-term use of amikacin in MDR-TB treatment was associated with a higher risk of the more severe forms of hearing loss compared to the use of kanamycin (adjusted odds ratio (OR)=4.0, 95% CI: 1.5–10.8). Patients co-infected with HIV (OR=3.4, 95% CI: 1.1–10.6), males (OR=4.5, 95%1.5–13.4) and those with lower baseline body weight (40–59 kg, OR=2.8, 95 %CI: 1.1–6.8), were most-at-risk of developing hearing loss. Consequently, we recommend that managers of MDR-TB treatment programmes should consider using kanamycin instead of amikacin for the treatment of MDR-TB. Second, national MDR-TB treatment programmes should invest more resources in building the capacity and the skills of health care personnel for the routine measurement of serum therapeutic drug levels, audiologic monitoring and the assessment of renal function of the most-at-risk patients treated with aminoglycosides. Targeted therapeutic drug monitoring of aminoglycosides during

MDR-TB treatment could minimize the occurrence of otologic and nephrologic adverse effects, without compromising therapeutic success.

Renal dysfunction is another important adverse reaction that may potentially limit the usefulness of aminoglycosides and capreomycin in MDR-TB treatment. This was studied in detail in **Chapter 3.3** where the renal function of MDR-TB patients who were treated with kanamycin (km) regimens or concomitantly with tenofovir (TDF) for HIV infection was monitored and compared by type of treatment exposure during the intensive phase of MDR-TB therapy. The study was done through a retrospective review of treatment records and laboratory tests of patients initiated on MDR-TB treatment from January to December 2014. The estimated pre/post-treatment glomerular filtration rates (eGFR) were compared using ANOVA-test. Renal insufficiency was defined as an eGFR of less than 60 ml/min/1.73 m^2. Km or TDF use and renal insufficiency was assessed using Kaplan Meier plots and Cox proportional hazards analysis.

In this study, renal function declined at similar rates among the MDR-TB patients who were treated with standard km-based regimens compared to those who were concomitantly treated for MDR-TB and HIV using both anti-TB and TDF-based antiretroviral regimens. The baseline mean eGFR for the three groups was comparable (p=0.24); 139.3±25.6 ml/min for the Km group (n=68), 131.1±25.7 ml/min for the Km+TDF group (n=44), and 134.2±34.4 ml/min for the Km+other group (n=23). After 8 months, the values had significantly declined to 104.8±37.5 ml/min (p<0.001); 101.5±38.3 ml/min (p<0.001) and 111.5±41.7 ml/min (p=0.01), respectively. Although not statistically significant, there was an observable excess risk of renal insufficiency among the patients who concomitantly received kanamycin plus tenofovir as compared to those who received kanamycin alone (HR=1.8; 0.7-4.1, p=0.20). Consequently, we emphasize that clinicians need to closely monitor the renal function of MDR-TB patients on kanamycin containing regimens, irrespective of HIV status, because of the increased risk of nephrotoxicity of kanamycin.

Chapter 4 is the general discussion and concluding chapter, where we elaborate further on how the safety of the old anti-TB drugs could be optimized. Several strategies could be used to achieve this goal. Clinicians should closely monitor patients on MDR-TB treatment to ensure that the adverse effects of second-line anti-TB drugs are recognized as quickly as possible so that remedial measures may be taken early enough. Serial audiologic and laboratory screening would be effective in achieving this. Shortening of the length of treatment will reduce exposure to ototoxic and nephrotoxic drugs. Where severe ototoxicity or nephrotoxicity inevitably occurs, patients should be provided with disability support and rehabilitative care. Implementing systematic drug utilization reviews (DUR), also called drug/medicine use evaluations (DUE or MUE) in MDR-TB treatment programs may help TB program managers to promote the safer and rational use of second-line anti-TB medicines.

It is also crucial to have strong, effective pharmacovigilance systems, especially considering the fast-tracked introduction of new anti-TB medicines. Additional safety data needs to be collected through ongoing post-marketing (Phase IV) safety studies for the new drugs. National TB control programmes should have strong pharmacovigilance systems for monitoring, detecting, and managing the adverse events that emerge during the use of the anti-TB drugs and related medicines. More financial, human and material resources need to be deployed to support the implementation and running of pharmacovigilance activities for TB control and other public health programs in low and middle income countries. Electronic patient registries and medical records could be utilized to efficiently answer specific pharmacovigilance questions. In addition to spontaneous reporting, active surveillance strategies should be used to monitor the safety of anti-TB, antiretroviral and other medicines in Namibia.

Several notable methodological challenges were encountered in the course of this research, including the low absolute numbers of patients infected with MDR-TB in Namibia; data availability; and data quality issues, such as missing data. In future, the use of electronic medical records and other electronic tools that are interoperable, promises to improve the availability and quality of data for pharmacovigilance and other health research.

In conclusion, this thesis showed that adverse events occur frequently in patients treated with current second-line anti-TB drugs. Most of these adverse events occur during the intensive phase of therapy and are preventable. Aminoglycosides and capreomycin are associated with potentially debilitating nephrotoxicity and ototoxicity, which may diminish patients' health-related quality of life. Other clinically important overlapping adverse events may occur in patients simultaneously taking antiretroviral medicines. Despite the safety and efficacy concerns with current second-line anti-TB drugs, these drugs are still needed in the treatment of MDR-TB. The focus, therefore, remains on ensuring the safer use of current and new anti-TB drugs. The monitoring and management of adverse events should be done regularly throughout MDR-TB therapy; and pharmacovigilance systems should be strengthened, including active surveillance. The long-term impact of adverse events on patients' health-related quality of life after completing MDR-TB treatment should be ascertained. More investment is needed in developing novel, safer and more effective anti-mycobacterial compounds.

SAMENVATTING

Tuberculose (TB) is een oude, dodelijke ziekte die zich de laatste jaren wereldwijd en sluipenderwijs steeds meer heeft gemanifesteerd. De niet eerder vertoonde opkomst en verspreiding van resistente stammen van *Mycobacterium tuberculosis*, zoals waargenomen in veel gebieden waaronder landen in Afrika bezuiden de Sahara, is daarbij vooral verontrustend. Tegen meerdere geneesmiddelen resistente TB (*multidrug resistant*, MDR-TB) en andere extreme vormen van multiresistente TB vormen een groeiend probleem dat de eerdere successen in de controle en eliminatie van TB ondermijnt. De wereldgezondheidsorganisatie (WHO) rapporteerde dat er alleen al in 2015 wereldwijd 480.000 nieuwe gevallen van TB optraden. De meerderheid hiervan trad op in India, China en Rusland. De belangrijkste oorzaak van geneesmiddelresistentie is het verkeerd gebruik van de huidige TB medicatie. Succespercentages van de behandeling van MDR-TB zijn volstrekt onvoldoende, slechts circa 52%. MDR-TB is behandelbaar met tweedelijns TB medicatie, als deze correct en volledig wordt ingenomen. De veiligheid en tolereerbaarheid van deze middelen is daarbij wel een grote zorg, aangezien hun gebruik veelvuldig leidt tot het optreden van bijwerkingen.

De behandeling van MDR-TB duurt lang, is complex en is geassocieerd met een heel scala aan bijwerkingen. Sommige van deze bijwerkingen, zoals ototoxiciteit, nefrotoxiciteit en levertoxiciteit, kunnen de kwaliteit van leven ernstig beperken. Het optreden van ernstige en serieuze bijwerkingen kan, evenals het verloop van de ziekte zelf, zowel tijdens als na de behandeling een grote impact hebben op het dagelijks functioneren van de patiënt. Hoewel het optreden van MDR-TB in Namibië de laatste jaren is afgenomen, blijft dit een veelvoorkomende infectie in dit land. Het veelvuldig en gelijktijdig optreden van besmetting met het humaan immunodeficiëntie virus (HIV) vormt een extra uitdaging voor de behandeling van beide aandoeningen.

Dit proefschrift beoogt het optreden van bijwerkingen van tweedelijns geneesmiddelen tegen TB in de dagelijkse klinische praktijk van het nationale MDR-TB programma in Namibië te bestuderen. De drie doelstellingen luidden: (i) het bepalen van de frequentie van, risicofactoren voor en management van het optreden van bijwerkingen van geneesmiddelen voor MDR-TB; (ii) het bepalen van de epidemiologie van ernstige bijwerkingen van aminoglycosiden bij patiënten met en zonder HIV die wel of niet behandeld worden met antiretrovirale therapie (ART); en (iii) het bepalen of er een associatie bestaat tussen het optreden van bijwerkingen en de kwaliteit van leven van de patiënt aan het einde van de behandeling voor MDR-TB.

Dit proefschrift bevat 4 hoofdstukken. **Hoofdstuk 1** is de introductie, waarin een algemeen overzicht over het onderwerp wordt gegeven, alsmede de doelstellingen van het proefschrift worden verwoord.

Veiligheid blijft een belangrijke zorg bij het gebruik van de huidige (oude) middelen bij de behandeling van MDR-TB. Daarom was het doel van **hoofdstuk 2.1** het in kaart brengen van de prevalentie, het profiel en de uitkomst van het optreden van bijwerkingen van deze geneesmiddelen en het bestuderen van de invloed van HIV co-infectie hierop. Dit was een cross-sectioneel, beschrijvend onderzoek, waarbij gebruik gemaakt werd van reeds verzamelde medische gegevens van alle 59 patiënten die voor DR-TB werden behandeld in de periode januari 2008 tot februari 2010 op een MDR-TB afdeling met 25 bedden. De benodigde gegevens werden uit medische statussen ge-extraheerd met behulp van een standaard formulier. In totaal traden 141 bijwerkingen op bij 90% (53/59) van de patiënten. Co-infectie met HIV trad op bij 53% (n=31). De prevalentie van gastro-intestinale bijwerkingen was 64%, tinnitus 45%, gewrichtspijn 28% en gehoorverlies 25%. De ernst van deze bijwerkingen varieerde en ze traden met name op in de intensieve fase van de MDR-TB behandeling. Hoewel de bijwerkingen in de meeste gevallen verdraagbaar waren voor patiënten, had 10% last van een bijwerking waar dit mogelijk niet het geval was. Sommige bijwerkingen, zoals buikpijn, uitslag, misselijkheid, gehoorverlies en gewrichtspijn, overlappen met bijwerkingen van ART en deze bijwerkingen kwamen inderdaad vaker voor bij patiënten met een HIV co-infectie. Artsen moeten de bijwerkingen van geneesmiddelen bij MDR-TB met name in de intensieve fase goed in de gaten houden en deze zo veel mogelijk bestrijden. Daarnaast moeten zij altijd rekening houden met de mogelijkheid dat bijwerkingen frequenter optreden, indien er sprake is van een HIV co-infectie.

In **hoofdstuk 2.2** vergeleken we daarom het optreden van bijwerkingen tussen patiënten die zowel voor MDR-TB als HIV werden behandeld en patiënten die alleen voor MDR-TB werden behandeld. Het belangrijkste doel van dit onderzoek was het vergelijken van absolute risico's en van risicofactoren voor vaak optredende bijwerkingen (optreden bij 20% van de patiënten of meer). Het betrof een retrospectief cohortonderzoek bij patiënten met MDR-TB die tussen januari 2008 en februari 2010 op de Kondja MDR-TB afdeling in Namibië werden behandeld. De gegevens waren afkomstig uit medische statussen en geanonimiseerd voor gebruik. De analyses waren beschrijvend en er zijn 2x2 kruistabellen gemaakt, uitgesplitst naar HIV status. Er werden 57 patiënten meegenomen in de analyses, waarvan 31 (53%) een HIV co-infectie had. Van de 18 bijwerkingen waar standaard navraag naar werd gedaan bij de patiënt kwamen tinnitus (40%), gewrichtspijn (26%), gehoorverlies (23%) en misselijkheid (21%) het meeste voor. Alleen buikpijn kwam significant vaker voor bij patiënten met een HIV co-infectie dan zonder HIV co-infectie (26% vs. 4%, p=0.02). Over het algemeen waren de risicofactoren voor bijwerkingen hetzelfde tussen de twee groepen. In sommige gevallen leek de HIV-status het effect van risicofactoren op het optreden van tinnitus, gewrichtspijn, gehoorverlies en misselijkheid te modificeren, maar door de lage sta-

tistische bewijskracht van het onderzoek valt dit niet met zekerheid te concluderen. Hiervoor is een groter en prospectief opgezet onderzoek nodig.

Hoofdstuk 2.3 bouwde voort op het onderzoek in **hoofdstuk 2.2** en gemaakte gebruik van dezelfde onderzoeksgegevens. Het doel was de incidentie te bepalen van symptomatische matig-ernstige tot ernstige bijwerkingen en de risico's en uitkomsten van deze bijwerkingen te vergelijken tussen patiënten met en zonder HIV co-infectie. Tijdens de behandeling van MDR-TB werd het ziektebeloop, het optreden van bijwerkingen, en de behandeling en uitkomst daarvan nauwkeurig gemonitord door de behandelaren. Van de 18 bijwerkingen waar standaard navraag naar werd gedaan bij de patiënt werd ook de ernst genoteerd. De benodigde gegevens werden achteraf geëxtraheerd aan de hand van een standaard formulier en zowel beschrijvend als bivariaat en met de Cox *proportional hazard* regressietechniek geanalyseerd. Daarbij werd gestratificeerd op HIV status. Van de 57 patiënten hadden 31 (53%) een HIV co-infectie. De cumulatieve incidentie van matig-ernstige en ernstige bijwerkingen bedroeg 46 per 100 patiënten. Patiënten met een HIV co-infectie ondervonden meer matig-ernstige en ernstige bijwerkingen dan patiënten zonder HIV co-infectie (mediaan 3 vs. 1 bijwerking, p=0.01). Zij hadden een vier keer verhoogd risico op het optreden van dergelijke bijwerkingen (hazard ratio (HR) 4.0; 95% betrouwbaarheidsinterval (BI) 1.5-10.5). Het optreden van matig-ernstige en ernstige bijwerkingen was de belangrijkste risicofactor voor het besluit van de arts om de dosering van het geneesmiddel te verlagen of de therapie te stoppen (relatief risico (RR) 3.8; 95% BI 1.2-11.8). Artsen moeten verschillende strategieën, waaronder dosisverlaging of het stoppen met medicatie, toepassen om discomfort en risico's ten gevolge van het gebruik van geneesmiddelen zo veel mogelijk te beperken. Daarnaast moeten systemen voor het melden en monitoren van bijwerkingen, zogenaamde farmacovigilantiesystemen, binnen TB programma's worden versterkt. Tot slot is een grotere studie nodig om de analyse van risicofactoren te herhalen en zo tot duidelijkere aanbevelingen te kunnen komen.

Of het optreden van bijwerkingen invloed heeft op de ervaren en aan de gezondheid gerelateerde kwaliteit van leven (*health related quality of life*, HRQoL) aan het eind van de behandeling van MDR-TB was het onderwerp van onderzoek in **hoofdstuk 2.4**. Patiënten in deze fase van hun behandeling werd in dit cross-sectionele onderzoek gevraagd mee te werken aan het invullen van een HRQoL vragenlijst. Het betrof hier de zogenaamde Short Form™ (SF-8) waarin acht vragen met een Likert-schaal zijn opgenomen (vier voor fysieke componenten en vier voor mentale componenten). Daarnaast kregen patiënten drie extra vragen over het optreden van bijwerkingen. De scores van de HRQoL waren op normen gebaseerd (gemiddelde=50, standaarddeviatie=0) met een spreiding van 20 (slechtste gezondheidstoestand) tot 80 (beste gezondheidstoestand), in plaats van de conventionele scores die van 0-100 gaan. De interne consistentie van de items werd bepaald aan de hand van de Cronbach's alfa. De scores werden op een beschrijvende

wijze gepresenteerd en de mogelijke associatie tussen de HRQoL score van een patiënt en het optreden van bijwerkingen werd bivariaat bestudeerd. Aan het onderzoek deden 36 patiënten mee, waaronder 20 mannen (56%) en de leeftijd varieerde van 17 tot 54 jaar (mediaan=40 jaar). Deze patiënten die net hun MDR-TB behandeling aan het afronden waren of deze net afgerond hadden scoorden hun HrQoL matig laag. De mediane score voor de vier fysieke componenten samen bedroeg 58.6 (range 35.3-60.5) en voor de vier mentale componenten samen 59.3 (26.6-61.9), wat duidt op een niet zo hoge waardering van de eigen gezondheidstoestand. Het optreden van bijwerkingen was niet geassocieerd met de HRQoL. De mediane HRQoL score bedroeg 56.8 (44.4-56.8) voor patiënten die 0-2 bijwerkingen rapporteerden en 55.2 (38.6-56.8) voor patiënten die 3 of meer bijwerkingen rapporteerden (p=0.34). Dit suggereert dat het mogelijk niet de therapie en het optreden van bijwerkingen, maar de aandoening zelf is die geassocieerd is met een verminderde kwaliteit van leven. Dit zou in een vervolgonderzoek verder bestudeerd moeten worden, waarbij de HRQoL bij het begin van en gedurende de behandeling wordt gemeten. Daarmee kunnen veranderingen in de HRQoL en de associatie met het optreden van bijwerkingen beter in worden onderzocht.

Op dit moment zijn amikacine, kanamycine en capreomycine een essentiële component van de behandeling van de intensieve fase van MDR-TB. Helaas zijn deze middelen, die per injectie worden gegeven, geassocieerd met het optreden van gehoorverlies en/of nierinsufficiëntie. De ototoxiciteit van aminoglycosides en capreomycine was het onderwerp van het onderzoek in **hoofdstuk 3.1**. Het doel van dit onderzoek was het bepalen van de associatie tussen het gebruik van streptomycine, amikacine, kanamycine en capreomycine voor TB en het rapporteren van bijwerkingen op het gebied van ototoxiciteit (doofheid of gehoorverlies, tinnitus en vertigo). Het tweede doel was het analyseren van patiëntenkarakteristieken en geografische factoren die van invloed zijn op het rapporteren van ototoxiciteit als bijwerking van de TB behandeling. Een case/non-case disproportionaliteitsanalyse werd uitgevoerd met individuele patiëntmeldingen (*individual case safety reports*, ICSRs) uit Vigibase® voor een van de genoemde middelen als onderdeel van de TB behandeling. Meldingen van ototoxiciteit vormden de cases, alle overige gemelde bijwerkingen de non-cases. Alle analyses werden uitgevoerd op het niveau van de combinatie van een bijwerking en geneesmiddel. Reporting odds ratios (RORs) en bijbehorende 95% BIs werden berekend met streptomycine als referentie. In juni 2014 bevatte Vigibase® 3361 combinaties van geneesmiddel-bijwerking (1693 ICSRs) waarin een van de vier geïncludeerde geneesmiddelen voor TB de mogelijke veroorzaker van de bijwerking was. Er waren 576 cases van doofheid, tinnitus of vertigo, de overige combinaties van geneesmiddel-bijwerking vormden de non-cases. Doofheid werd voor deze middelen als onderdeel van de TB behandeling vaker gerapporteerd bij gebruik van amikacine (ROR 9.3; 95% BI 3.8-23.0) en kanamycine (ROR 4.3; 95% BI 1.3-14.2) dan bij streptomycine. Aan de andere kant was de rapportage van vertigo invers

gerelateerd aan het gebruik van capreomycine (ROR 0.1; 95% BI 0.01-0.4). De leeftijd en het geslacht van de patiënt hadden in dit onderzoek geen effect op het melden van ototoxiciteit. Wel was er een opvallend geografisch verschil in meldingen. Vergeleken met Afrika was er een verhoogd risico op meldingen van ototoxiciteit als bijwerking bij deze middelen als onderdeel van de TB behandeling in Noord- en Zuid-Amerika (ROR 4.0; 95% BI 1.7-9.3), Azië (ROR 5.1; 95% BI 2.4-11.0) en Europa (ROR 4.8; 95% BI 2.2-10.4). Doofheid of tinnitus was de meest gerapporteerde vorm van ototoxiciteit in Noord- en Zuid-Amerika (ROR 5.0; 95% BI 1.4-17.3), terwijl vertigo het meest gerapporteerd werd door landen uit Azië (ROR 6.6; 95% BI 2.4-17.9). In Europa was er nauwelijks verschil in de rapportage van meldingen van doofheid en tinnitus (ROR 3.8; 95% BI 1.2-12.4) en vertigo (ROR 4.6; 95% BI 1.7-12.6). Deze resultaten kunnen een weerspiegeling zijn van de wereldwijde epidemiologie van TB, maar ook van de mate van ontwikkeling en het functioneren van meldingssystemen in landen die participeren in het WHO programma voor bewaking van de veiligheid van geneesmiddelen.

Amikacine en kanamycine vormen voorlopig de pijler van de behandeling van MDR-TB, vooral in lage inkomenslanden waar de ziektelast door MDR-TB het hoogste is. Zij kunnen beide echter dosisafhankelijke irreversibele schade aan het gehoor toebrengen, indien zij niet juist worden gebruikt. In het licht hiervan werd in **hoofdstuk 3.2** de cumulatieve incidentie van gehoorverlies vergeleken tussen patiënten die therapieën met amikacine of met kanamycine gebruikten. Daarnaast werd in dit retrospectieve co-hortonderzoek (n=353) in Namibië getracht vast te stellen welke patiënten het meeste risico op deze bijwerking hebben. Hiertoe werden gegevens verkregen van patiënten die werden behandeld voor MDR-TB en in het kader hiervan routine metingen van hun gehoor ondergingen in de periode juni 2004 tot maart 2014. De primaire uitkomst van dit onderzoek was het optreden van enige vorm van gehoorschade. Percentages werden vergeleken met behulp van de Chi-kwadraattoets. Een gestratificeerde en logistische regressie werd uitgevoerd om het risico op gehoorschade te bepalen en patiënten met het meeste risico te identificeren (effectmodificatie). Alle 353 patiënten hadden een normaal gehoor bij start van de therapie en 46% van de patiënten had een HIV co-infectie. De cumulatieve incidentie van enige vorm van gehoorverlies was 58%. Sommige vormen waren matig in ernst (23%), anderen waren matig-ernstig (16%), ernstig (10%) of zeer ernstig (15%). Slechts 32% van het gehoorverlies was mild. Het langdurig gebruik van amikacine als onderdeel van de behandeling van MDR-TB was geassocieerd met een hoger risico op de meer ernstige vormen van gehoorverlies dan het gebruik van kanamycine (gecorrigeerde odds ratio (OR) 4.0; 95% BI 1.5-10.8). Patiënten met een HIV co-infectie (OR 3.4; 95% BI 1.1-10.6), mannen (OR 4.5; 95% BI 1.5-13.4) en patiënten met een laag gewicht bij de start van de behandeling (40-59 kilogram, OR 2.8; 95% BI 1.1-6.8) hadden het grootste risico om gehoorschade te ontwikkelen. Daarom wordt aangeraden om binnen MDR-TB behandelprogramma's

kanamycine voor te schrijven in plaats van amikacine. Daarnaast zou binnen deze programma's geïnvesteerd moeten worden in het opbouwen van capaciteit en vaardigheden onder medisch personeel om routinemetingen, zoals therapeutische spiegelbepalingen, audiologische metingen en nierfunctie, te kunnen verrichten bij patiënten met de hoogste risico's. De inzet van therapeutische spiegelbepalingen van aminoglycosides zou het risico op het optreden van nadelige effecten op het gehoor en de nier kunnen beperken, zonder dat de kans op therapeutische succes vermindert.

Verminderde nierfunctie is een andere belangrijke bijwerking die de toepasbaarheid van aminoglycosides en capreomycine mogelijk in de weg staat. Dit onderwerp werd in meer detail bestudeerd in **hoofdstuk 3.3**. Hierin werd de nierfunctie van patiënten die met kanamycine (km) werden behandeld in de intensive fase van MDR-TB vergeleken met de nierfunctie van patiënten die tegelijkertijd werden behandeld met tenofovir (TDF) voor HIV. Voor dit retrospectieve cohortonderzoek werden gegevens over geneesmiddelgebruik en laboratoriumuitslagen gebruikt van patiënten die startten met hun MDR-TB behandeling in de periode januari tot december 2014. De berekende glomerulaire filtratiesnelheid (eGFR) voor en na behandeling werd vergeleken met een ANOVA-test. Nierinsufficiëntie werd gedefinieerd als een eGFR van 60 ml/min/1.73 m^2 of minder. De relatie tussen km of km+TDF gebruik en het optreden van nierinsufficiëntie werd bestudeerd aan de hand van Kaplan-Meier curves en met behulp van Cox *proportional hazard* regressieanalyse. In dit onderzoek ging de nierfunctie in alle patiëntengroepen in dezelfde mate achteruit. Bij start van de behandeling was de eGFR voor alle groepen gelijk (p=0.24); 139.3±25.6 ml/min voor patiënten die met kanamycine werden behandeld (n=68), 131.1±25.7 ml/min voor patiënten die gelijktijdig TDF gebruikten (n=44) en 134.2±34.4 ml/min voor patiënten die gelijktijdig andere medicatie voor HIV gebruikten maar geen TDF (n=23). Na 8 maanden waren deze waarden significant lager, respectievelijk 104.8±37.5 ml/min (p<0.001), 101.5±38.3 ml/min (p<0.001) en 111.5±41.7 ml/min (p=0.01). Een verhoogd risico op nierinsufficiëntie kon niet worden uitgesloten bij patiënten die kanamycine en tenofovir gebruikten ten opzichte van patiënten die alleen kanamycine gebruikten (HR 1.8; 95% BI 0.7-4.1). Daarom wordt aangeraden de nierfunctie nauwlettend in de gaten te houden bij patiënten die kanamycine gebruiken, ongeacht hun HIV status.

Hoofdstuk 4 is de algemene discussie en het afsluitende hoofdstuk van het proefschrift, waarin verder uiteen wordt gezet hoe de veiligheid van oude geneesmiddelen voor TB kan worden geoptimaliseerd. Artsen moeten patiënten nauwlettend in de gaten houden om te waarborgen dat bijwerkingen in een zo vroeg mogelijk stadium worden gesignaleerd, zodat de juiste maatregelen kunnen worden genomen. Routinematig meten van de gehoorfunctie en laboratoriumwaardes kan hieraan bijdragen. Het inkorten van de lengte van de behandeling kan de blootstelling aan oto- en nefrotoxische geneesmiddelen verminderen. Indien ernstige gehoorschade of nierinsuf-

ficiëntie optreedt, moeten patiënten zo goed mogelijk worden ondersteund bij hun herstel en revalidatie. Het implementeren van systematische medicatiebeoordelingen binnen MDR-TB behandelprogramma's kan tot slot een bijdrage leveren aan veiliger en rationeel gebruik van tweedelijns medicatie tegen TB.

Het is van cruciaal belang een effectief en goed functionerend farmacovigilantiesysteem te hebben, ook met het oog op de versnelde introductie van nieuwe geneesmiddelen tegen TB. Aanvullende gegevens over de veiligheid van dergelijke middelen moeten worden verzameld tijdens postmarketing onderzoek (fase 4 onderzoek). Binnen nationale TB programma's is een dergelijk goed functionerend systeem belangrijk voor het ontdekken, volgen en behandelen van bijwerkingen die tijdens de behandeling van TB en daaraan gerelateerde aandoeningen optreden. Er zijn meer investeringen nodig, zowel financieel als mensen en materialen, om de implementatie en het onderhouden van activiteiten op het gebied van farmacovigilantie in lage en middeninkomenslanden mogelijk te maken. Elektronische patiëntregisters en andere medische gegevens kunnen worden gebruikt om vraagstukken op dit gebied op een efficiënte wijze te beantwoorden. Daarnaast moeten in Namibië niet alleen spontane meldingen, maar ook actieve strategieën op het gebied van geneesmiddelenbewaking worden ingezet om de veiligheid van geneesmiddelen in zijn algemeenheid en TB en HIV in het bijzonder te bewaken.

In het bovenstaande onderzoek moest worden omgegaan met verschillende methodologische uitdagingen, zoals de kleine aantallen patiënten met MDR-TB in Namibië, de beschikbaarheid van gegevens en de kwaliteit van gegevens, waaronder missende data. In de toekomst moet het gebruik van (te koppelen en) elektronisch beschikbare medische gegevens leiden tot een verbetering van de beschikbaarheid en kwaliteit van gegevens voor dit type onderzoek en ander onderzoek binnen de gezondheidszorg.

Concluderend wordt gesteld dat dit proefschrift heeft aangetoond dat bijwerkingen vaak voorkomen bij patiënten die met tweedelijns geneesmiddelen tegen TB worden behandeld. De meeste van deze bijwerkingen treden op tijdens de intensieve fase van de behandeling en zijn vermijdbaar. Aminoglycosides en capreomycine zijn geassocieerd met nefrotoxiciteit en ototoxiciteit, wat de kwaliteit van leven van de patiënt kan verminderen. Bij patiënten die ook antiretrovirale geneesmiddelen gebruiken kunnen klinisch belangrijke bijwerkingen overlappen. Ondanks de zorgen over de veiligheid en effectiviteit van deze oude middelen tegen TB, zijn deze nog steeds onontbeerlijk voor een adequate behandeling van MDR-TB. De focus moet daarom liggen op veiliger gebruik van deze middelen. Het volgen en behandelen van bijwerkingen moet regelmatig worden gedaan tijdens de behandeling en farmacovigilantiesystemen moeten daartoe worden versterkt. Lange termijneffecten van bijwerkingen op de kwaliteit van leven moeten worden vastgesteld. Tot slot zijn meer investeringen nodig om nieuwe, veiligere en effectievere geneesmiddelen voor TB te ontwikkelen.

ADDENDUM

Acknowledgments

List of co-authors

List of publications

About the author

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List of publications

Included in this thesis

1. Sagwa E, Mantel-Teeuwisse AK, Ruswa N, et al. The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. *South Med Rev.* 2012;5(1):6-13.

2. Sagwa E, Ruswa N, Musasa JP, Mantel-Teeuwisse AK. Adverse events during treatment of drug-resistant tuberculosis: a comparison between patients with or without human immunodeficiency virus co-infection. *Drug Saf.* 2013;36(11):1087-1096.

3. Sagwa EL, Mantel-Teeuwisse AK, Ruswa NC. Occurrence and clinical management of moderate-to-severe adverse events during drug-resistant tuberculosis treatment: a retrospective cohort study. *J Pharm policy Pract.* 2014;7(1):14.

4. Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Leufkens HGM, Mantel-Teeuwisse AK. Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. *BMC Pharmacol Toxicol.* 2015;16(1):36.

5. Sagwa E, Ruswa N, Mavhunga F, Rennie T, Leufkens H, Mantel-Teeuwisse A. Adverse events and patients' perceived health-related quality of life at the end of multidrug-resistant tuberculosis treatment in Namibia. *Patient Prefer Adherence.* 2016;10:2369-2377.

6. Sagwa EL, Souverein PC, Ribeiro I, Leufkens HGM, Mantel-Teeuwisse AK. Differences in VigiBase® reporting of aminoglycoside and capreomycin-suspected ototoxicity during tuberculosis treatment. *Pharmacoepidemiol Drug Saf. 2017;26(1):1-8.*

7. Sagwa EL, Ruswa N, Mavhunga F, et al. Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with tenofovir for HIV. *submitted.*

Unrelated to this thesis

1. Corbell C, Katjitae I, Mengistu A, et al. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. *Pharmacoepidemiol Drug Saf.* 2012;21(4):407-414.

2. Mann M, Mengistu A, Gaeseb J, et al. Sentinel site active surveillance of safety of first-line antiretroviral medicines in Namibia. *Pharmacoepidemiol Drug Saf.* 2016;25(9):1052-1060.

3. Mann M, Mengistu A, Gaeseb J, et al. Active Surveillance versus Spontaneous Reporting for First-Line Antiretroviral Medicines in Namibia: A Cost–Utility Analysis. *Drug Saf.* 2016;39(9):859-872.

Publications

About the author

Born in Kakamega County in Kenya, Evans Sagwa is a sea-soned pharmaceutical management expert, with more than 15 years of experience in pharmaceutical management in sub-Saharan Africa. His expertise spans pharmaceutical policy analysis, pharmaceutical services management, medicines safety management, pharmacoeconomics and pharmacy practice research. He is well trained in strategic management, management science, health services quality management, management consulting, project management and systems capacity building.

At the time of publishing his Doctoral thesis, Evans was working for Management Sciences for Health (MSH), a reputable international US-based Non-Governmental Organization (NGO), where he was the Country Director for the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) project and the Supply Chain Management System (SCMS) project in Namibia. In this role, he led and man-aged a team of local and international technical advisors and consultants working on various aspects of pharmaceutical systems strengthening, including the strengthening of pharmacovigilance systems as well as spearheading the setting up of the School of Pharmacy at the University of Namibia. He also holds a Master of Public Health (MPH) from the University of the Western Cape in South Africa, a Master of Business Adminis-tration (MBA) and a Bachelor of Pharmacy, both from the University of Nairobi in Kenya. He speaks Luhya, Swahili, English, some French and some Kinyarwanda. Together with Clemence, his lovely and adoring wife, they have two daughters (Bianca and Lovisa) and a son (Caleb). He likes cycling the mountain bike for leisure and for physical fitness; and playing the drums for Gospel rock music. He is a member of the Christian Revival Church (CRC) in Windhoek, Namibia.

"I can do all this through Him who gives me strength"
(Philippians 4:13, New International Version)

Aubot the Author