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ORIGINAL RESEARCH ARTICLE

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 (DR) tuberculosis (TB) co-infection, interactions and adverse events associated with second-line anti-TB and antiretroviral medicines pose a unique challenge in the treatment of both infections.

Objective The main objective of this 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 This was a retrospective cohort analysis of patients treated for DR-TB between January 2008 and February 2010 at the Kondja DR-TB ward in Walvis Bay, Namibia. Data were anonymously collected from patients' treatment records, using a structured form. The data were then analyzed using descriptive statistics, while 2×2 contingency tables stratified by HIV status were employed to examine specific risk factor and adverse event relationships, using Epi Info 3.4.3 statistical software.

Eighteen adverse events were studied but, because of 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 a treatment period of <4 weeks; treatment with any highly active antiretroviral therapy (HAART) regimen; specific treatment with a zidovudine (AZT)-based HAART regimen, a cycloserine-based DR-TB regimen or an amikacin-based DR-TB regimen; female gender; baseline body weight ≤45 kg; and age 30 ≥years.

Results Of the 57 DR-TB patients who were included in the analysis, 31 (53 %) were co-infected with HIV. When stratified by HIV status, DR-TB patients had similar exposure to specific DR-TB medicines and comparable demographic and clinical characteristics, except for age, as 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 for abdominal pain was there a statistically significant difference in the risk of occurrence between HIV-infected patients and HIV-uninfected patients (26 versus 4 %, $P = 0.02$).

The risk ratios (RRs) for the association between treatment with a cycloserine-based DR-TB regimen and occurrence of joint pain did not differ much between HIV-infected and HIV-uninfected patients (RR 4.3 in HIV-infected patients, $P = 0.03$; RR 5 in HIV-uninfected patients, $P = 0.08$). Similarly, although some differences in the RRs were observed between the two HIV status groups, the

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differences were not statistically significant for tinnitus, hearing loss or 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 were inconclusive.

Conclusion Generally, the absolute risks and risk factors for adverse events were similar between HIV-infected and HIV-uninfected patients treated for DR-TB 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 statistical 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.

1 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] and the TB case notification rate was 589 per 100,000 of population, while 56 % of TB patients were co-infected with HIV [3]. Of concern is the high prevalence of drug-resistant (DR) TB, with 285 cases being 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 occurrence of serious adverse events, such as severe hepatic, renal, auditory and vestibular toxicity [6–9]. This problem is compounded in patients concurrently being treated for both DR-TB and HIV infection because of the potential overlap of anti-TB and antiretroviral 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 multidrug-resistant (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-TB medications because of the serious adverse events associated with anti-TB medications [9]. Lorent et al. [14] 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 TB in Rwanda. 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 possible adverse events [4, 5]. In a previous paper [15], we showed that adverse effects are common during treatment of DR-TB in Namibia, particularly in the intensive phase of therapy. In the same paper, we also reported that some 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 an increased risk of experiencing an adverse event during TB chemotherapy. A study conducted in Canada found that occurrence of any major adverse event with first-line TB therapy was associated with being female, being over 60 years of age, being of Asian descent and 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 have been 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 DR-TB, especially regarding the influence of HIV infection and antiretroviral therapy. The high prevalence of HIV and DR-TB and the frequent co-infection with 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.

1.1 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.

2 Methods

2.1 Study Design and Population

We conducted a retrospective cohort analysis of all patients treated for DR-TB with individualized second-line anti-TB regimens at the Kondja TB ward (a specialized public-sector DR-TB treatment facility in Walvis Bay, Namibia) in the period between 1 January 2008 and 24 February 2010 inclusive. Patients were followed up from the time they were initiated on second-line anti-TB medication to the earliest of either occurrence of each of the adverse events of interest, or death, loss to follow up or the study end date. During the follow-up period, all patients diagnosed with any form of TB were routinely counselled and tested for HIV co-infection,

and this information was recorded in their medical files [3]. The details of treatment of DR-TB 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.

2.2 Data Collection

We reviewed patients' treatment charts and collected the required data, using a structured data extraction form. The data included each patient's age, gender, baseline body weight, HIV status, specific drugs in the individualized DR-TB regimen, the antiretroviral therapy regimen, the type of *Mycobacterium tuberculosis* drug resistance, the length of time on DR-TB treatment (the intensive phase and the 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 TB and leprosy programme as part of the patient DR-TB treatment monitoring chart. This form listed 18 adverse events—namely, abdominal pain, constipation, hearing loss (decreased hearing), depression, diarrhoea, dizziness, fatigue, fever, headache, joint pain, nausea, neuropathy, psychosis, rash, tinnitus, tremors, vision changes and vomiting [5].

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

2.3 Data Analysis

The data were entered into Epi Info Version 3.4.3 software (November 2007; Centers for Disease Control and Prevention, Atlanta, GA, 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 as either binary or multiple responses to facilitate computerized analysis. Microsoft Excel® software (Microsoft Office 2010; Microsoft Corporation, Redmond, WA, USA) was subsequently used to draw tables and charts.

We used descriptive statistics to analyse the frequencies and distributions of the various variables that were 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 means and standard deviations (SDs), and medians and interquartile ranges (IQRs), 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 χ^2, Mantel–Haensel χ^2 or 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 were reported.

Specifically, we sought to examine the following factors for their influence on the risk of the commonly occurring clinically significant adverse events: the 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 on the basis of our review of the literature, where similar risk factors have previously been documented [11, 12, 14, 16, 17, 26]. We conducted bivariate analysis using 2×2 contingency tables to calculate the risk ratio (RR) of the association of specific risk factor and adverse event pairs at the 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 of the 18 adverse events that are routinely monitored during DR-TB treatment in Namibia, we could not examine risk factors for each of them because of the small absolute counts of 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 larger absolute counts to enable 2×2 cross-tabulation and stratified statistical analysis. For each of the four adverse events of interest, the overall cohort RRs, stratum-specific RRs and *P* values were reported. The overall and stratum-specific RRs were compared for effect modification. In all of the analyses, two-sided *P* values of less than 0.05 were considered statistically significant.

3 Results

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

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

Of the 18 studied adverse events, only for abdominal pain was the risk of occurrence significantly greater in HIV-infected patients than in HIV-uninfected patients (26 versus 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.

3.1 Tinnitus

Overall, 23 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 was 12/31 (39 %) in HIV-infected patients and 11/26 (42 %) in HIV-uninfected patients. There was no statistically significant difference in risk between the two HIV subgroups ($P = 0.78$) [Table 3]. The specific risk factors for tinnitus were similar in 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 RRs were similar for HIV-infected and HIV-uninfected patients, with wide, overlapping confidence intervals (CIs).

3.2 Hearing Loss

Overall, 13 of the 57 patients (23 %) complained of hearing loss. Of these 13 patients, 8/31 (26 %) were HIV infected and 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 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 RRs were similar for HIV-infected and HIV-uninfected patients, with wide, overlapping CIs.

3.3 Joint Pain

In total, 15 of the 57 studied patients (26 %) experienced joint pain. Of these 15 patients, 9/31 (29 %) were HIV

Table 1 Demographic and clinical characteristics of drug-resistant (DR) tuberculosis (TB) patients, stratified by human immunodeficiency virus (HIV) status

Characteristic	HIV status, $N = 57$		
	HIV-infected patients, $n = 31$	HIV-uninfected patients, $n = 26$	P value
Gender: male [n (%)]	19 (61)	17 (65)	0.41
Age [years; mean ± SD (range)]	37.3 ± 7.6 (21–55)	30.8 ± 10.0 (11–53)	0.007[a]
Weight [kg; mean ± SD (range)]	52.7 ± 12.5 (24.2–68.7)	52.2 ± 10.5 (29–92)	0.38
Use of any HAART regimen [n (%)]	13 (42)	NA	–
Use of AZT-based HAART regimen [n (%)]	5 (16)	NA	–
Previous TB treatment [n (%)]	28 (94)	24 (92)	0.62
MDR-TB [n (%)]	17 (55)	18 (69)	–
PDR-TB [n (%)]	11 (35)	7 (27)	–
XDR-TB [n (%)]	1 (3)	0 (0)	–
Duration of intensive phase therapy [days; 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)	–

AZT zidovudine, *HAART* highly active antiretroviral therapy, *IQR* interquartile range, *MDR* multidrug-resistant, *PDR* polydrug-resistant, *SD* standard deviation, *XDR* extensively resistant

[a] Statistically significant P value

Table 2 Exposure to second-line anti-tuberculosis (TB) medicines, stratified by human immunodeficiency virus (HIV) status and weight-based dosing protocol

Anti-TB drug	Patients exposed [*n* (%)]		Dosing by weight class[a]			
	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	1,000–1,750 mg daily	1,750–2,000 mg daily	2,000–2,500 mg daily
Ethionamide	26 (84)	26 (100)	15–20 mg/kg daily	500 mg	750 mg	750–1,000 mg
Levofloxacin	19 (61)	18 (69)	Usual adult dose for MDR-TB is 750 mg	750 mg	750 mg	750–1,000 mg
Ethambutol	19 (61)	16 (62)	25 mg/kg daily	800–1,200 mg daily	1,200–1,600 mg daily	1,600–2,000 mg daily
Kanamycin	16 (52)	14 (54)	15–20 mg/kg daily	500–750 mg	1,000 mg	1,000 mg
Cycloserine	14 (45)	13 (50)	15–20 mg/kg daily	500 mg	750 mg	750–1,000 mg
Amikacin	12 (39)	9 (35)	15–20 mg/kg daily	500–750 mg	1,000 mg	1,000 mg
Ciprofloxacin	11 (35)	8 (31)	20–30 mg/kg daily	1,500 mg	1,500 mg	1,500 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	1,000 mg	1,000 mg
Isoniazid	3 (10)	1 (4)	4–mg/kg daily or 8–12 mg 3 times weekly	200–300 mg daily or 450–600 mg 3 times weekly	300 mg daily or 600 mg 3 times weekly	300 mg daily or 600 mg 3 times weekly
Streptomycin	1 (3)	2 (8)	15–20 mg/kg daily	500–750 mg	1,000 mg	1,000 mg
Clofazimine	1 (3)	0 (0)	Efficacy and dosing in treatment of DR-TB not fully determined			
Amoxicillin/clavulanic acid	1 (3)	0 (0)	Efficacy and dosing in treatment of DR-TB not fully determined			

DR drug-resistant, *MDR* multidrug-resistant

[a] *Source:* World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2006: 147-8

infected and 6/26 (23 %) were HIV uninfected. The difference in the absolute risk of experiencing joint pain between HIV-infected and 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 RR remained virtually unchanged between the two HIV status groups (RR 4.3 in HIV-infected patients, $P = 0.03$; RR 5 in HIV-uninfected patients, $P = 0.08$), 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 significantly associated with occurrence of joint pain in our cohort (levofloxacin exposure RR 1.5, 95 % CI 0.5–4.1, $P = 0.32$; 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 RR for the stratum of HIV-infected patients was more pronounced (RR 3.2, 95 % CI 1.0–10.3, $P = 0.05$) than that for HIV-uninfected patients (RR 0.4, 95 % CI 0.1–3.1, $P = 0.35$).

3.4 Nausea

In total, 12 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 subgroups ($P = 0.34$), as shown in Table 3. We found that none of the risk factors were significantly associated with 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 occurrence of nausea. The relationship was more pronounced in HIV-infected patients (RR 5.1, 95 % CI 0.7–36.9, $P = 0.06$) than in HIV-uninfected patients (RR 0.4, 95 % CI 0.1–3.3, $P = 0.38$).

Table 3 Comparison of the risks of occurrence of 18 types of adverse event, stratified by human immunodeficiency virus (HIV) status

Adverse event	Cumulative incidence for cohort [*n*/57 (%)]	HIV-infected patients [*n*/31 (%)]	HIV-uninfected patients [*n*/26 (%)]	*P* value[a]
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[b]
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
Diarrhoea	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)	NA

NA not applicable

[a] *P* values are for the χ^2 test comparing two proportions

[b] Statistically significant *P* value

4 Discussion

To the best of our knowledge, this is the first ever documented study in Namibia that has analysed the risks and risk factors for occurrence of adverse events among patients treated for DR-TB, stratified by HIV infection status. When stratified by HIV status, the 57 patients treated for DR-TB in our cohort had a similar profile of exposure to specific DR-TB medicines and similar demographic and clinical characteristics, 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 RRs for the association between treatment with a cycloserine-based DR-TB regimen and occurrence of joint pain did not differ much between HIV-infected and HIV-uninfected patients.

The patients included in our cohort were generally young adults in their thirties, which precluded us from examining the influence of either very young age or advanced age on 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 the Ministry of Health and Social Services in Namibia [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-TB 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 a study conducted in India by Isaakidis et al. [11], patients were treated with either

Table 4 Risk factor analysis for occurrence of tinnitus, stratified by human immunodeficiency virus (HIV) status

Risk factor	RR (95 % CI), *P* value	Stratum-specific RR (95 % CI), *P* value	
	Overall cohort of DR-TB patients, $n = 57$	HIV-infected DR-TB patients, $n = 31$	HIV-uninfected DR-TB patients, $n = 26$
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. Use of any HAART regimen	1.8 (0.7–5.2), $P = 0.21$	1.8 (0.7–5.2), $P = 0.21$	NA
3. Use of AZT-based HAART regimen	0.8 (0.2–2.9), $P = 0.59$	0.9 (0.2–2.9), $P = 0.59$	NA
4. Use of 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. Use of 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 ≤45 kg	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), $P = 0.47$

AZT zidovudine, *CI* confidence interval, *DR* drug-resistant, *HAART* highly active antiretroviral therapy, *NA* not applicable, *RR* risk ratio, *TB* tuberculosis

Table 5 Risk factor analysis for occurrence of hearing loss, stratified by human immunodeficiency virus (HIV) status

Risk factor	RR (95 % CI), *P* value	Stratum-specific RR (95 % CI), *P* value	
	Overall cohort of DR-TB patients, $n = 57$	HIV-infected DR-TB patients, $n = 31$	HIV-uninfected DR-TB patients, $n = 26$
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. Use of any HAART regimen	0.5 (0.1–2.1), $P = 0.29$	0.5 (0.1–2.1), $P = 0.29$	NA
3. Use of AZT-based HAART regimen	0.0, $P = 0.36$	0.0, $P = 0.36$	NA
4. Use of 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. Use of 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 ≤45 kg	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), $P = 0.58$

AZT zidovudine, *CI* confidence interval, *DR* drug-resistant, *HAART* highly active antiretroviral therapy, *NA* not applicable, *RR* risk ratio, *TB* tuberculosis

Table 6 Risk factor analysis for occurrence of joint pain, stratified by human immunodeficiency virus (HIV) status

Risk factor	RR (95 % CI), *P* value	Stratum-specific RR (95 % CI), *P* value	
	Overall cohort of DR-TB patients, $n = 57$	HIV-infected DR-TB patients, $n = 31$	HIV-uninfected DR-TB patients, $n = 26$
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. Use of any HAART regimen	1.2 (0.4–4.0), $P = 0.53$	1.2 (0.4–4.0), $P = 0.53$	NA
3. Use of AZT-based HAART regimen	0.5 (0.1–3.8), $P = 0.49$	0.5 (0.1–3.8), $P = 0.48$	NA
4. Use of cycloserine-based DR-TB regimen	4.4 (1.4–14.1), $P = 0.004$[a]	4.3 (1.04–17.3), $P = 0.03$[a]	5.0 (0.7–37.1), $P = 0.08$
5. Use of 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 ≤45 kg	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), $P = 0.40$

AZT zidovudine, *CI* confidence interval, *DR* drug-resistant, *HAART* highly active antiretroviral therapy, *NA* not applicable, *RR* risk ratio, *TB* tuberculosis

[a] Statistically significant *P* value

kanamycin (57 %) or capreomycin (57 %) but not amikacin. Similarly, in a study conducted in Turkey by Törün et al. [7], amikacin was administered in about 80 % of patients, capreomycin in 8 % and kanamycin in 5 %. In another study reported from Russia by Shin et al. [8], most patients were treated with either capreomycin (63 %) or kanamycin (47 %), and only 0.8 % of patients were treated with amikacin. Such differences in the usage patterns of specific second-line anti-TB medicines may explain differences in the frequency and magnitude of the occurrence of specific adverse events across different 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. [11], who found that, overall, gastrointestinal symptoms were the most common adverse event in their cohort of HIV co-infected patients. 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 were 39 and 26 %, respectively, while in HIV-uninfected patients, they were 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, Törün et al. [7] studied a cohort of 263 HIV-uninfected patients treated for MDR-TB in Turkey, using either amikacin- or kanamycin-based

Table 7 Risk factor analysis for occurrence of nausea, stratified by human immunodeficiency virus (HIV) status

Risk factor	RR (95 % CI), *P* value	Stratum-specific RR (95 % CI), *P* value	
	Overall cohort of DR-TB patients, $n = 57$	HIV-infected DR-TB patients, $n = 31$	HIV-uninfected DR-TB patients, $n = 26$
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. Use of any HAART regimen	1.6 (0.4–6.1), $P = 0.37$	1.6 (0.4–6.1), $P = 0.37$	NA
3. Use of AZT-based HAART regimen	4.8 (0.7–34.4), $P = 0.12$	4.8 (0.7–34.4), $P = 0.12$	NA
4. Use of 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. Use of 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 ≤45 kg	1.2 (0.4–3.6), $P = 0.53$	2.2 (0.7–6.7), $P = 0.21$	0.0, $P = 0.32$
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), $P = 0.24$

AZT zidovudine, *CI* confidence interval, *DR* drug-resistant, *HAART* highly active antiretroviral therapy, *NA* not applicable, *RR* risk ratio, *TB* tuberculosis

regimens, and found that 42 % of the patients experienced ototoxicity. 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 a cohort of 244 MDR-TB patients predominantly treated with capreomycin-based regimens in Tomsk, Russia, the risk of ototoxicity was much lower, at 16 % [8]. The risk of ototoxicity in a cohort of 67 patients co-infected with HIV and MDR-TB 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 the reported risks of ototoxicity across different 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 with 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 TB treatment guidelines and also from variations 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-TB drugs (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-TB 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 wide variation in the risk of joint pain reported in the literature. For instance, Shin et al. [8] reported a higher risk (47 %) of joint pain (arthralgia) in a Russian cohort of MDR-TB patients, while Bloss et al. [9] reported a lower risk (13 %) in a cohort of 1,027 patients in Latvia. A similar low risk (11 %) of joint pain among HIV-uninfected patients was reported by Törün et al. [7]. In the Philippines, Tupasi et al. [34] reported risks of 31 % for minor joint pain and 17 % for arthritis/gout. This variation could be partly attributed to differences in the definition of joint pain and the grading of severity that was utilized across the different settings.

Our finding that treatment of DR-TB using cycloserine-containing regimens is associated with 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 worth noting 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, rather than to pyrazinamide. In this cohort, neither use of levofloxacin nor use of pyrazinamide-containing regimens were statistically significant risk factors for 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 expectations, given that nausea is common during use of zidovudine (AZT) [35]. Failure to detect a statistically significant difference between the two HIV subgroups may have been due to the low statistical 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 CIs were inconclusive. Therefore we would prefer to exercise caution in interpreting findings from the exploration of effect modification in this study.

Our study had several limitations. The small sample size and the retrospective nature of the study were its biggest limitations. Specifically, the RRs listed in Tables 4, 5, 6 and 7 are quite wide, largely because of the small counts within each cell of the contingency tables. Because of the retrospective study design, HIV-treatment–related adverse events were not included because they were not routinely captured in 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 resulted in underestimation or overestimation of 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 DR-TB 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 receiving concomitant treatment for DR-TB and HIV infection. The documentation of 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 can be better understood. Adherence to the TB treatment guidelines by clinicians should also be reinforced.

5 Conclusion

Generally, the absolute risks and risk factors for adverse events were similar between HIV-infected and HIV-uninfected patients treated for DR-TB 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 statistical 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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Author contributions Evans Sagwa conceived and designed the study; collected and analyzed the data; and drafted, finalized and submitted the manuscript. Nunurai Ruswa and Jean Paul Musasa reviewed the study protocol and manuscript. Aukje Mantel-Teeuwisse contributed to the interpretation of the study findings, provided guidance on writing of the manuscript and critically reviewed all drafts of the manuscript.

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