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Prevalence and predictors of adverse events among patients receiving Multi-Drug Resistant Tuberculosis treatment at Kibong'oto Infectious Disease Hospital, Tanzania: A retrospective study

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Abstract

Background: Multidrug-resistant tuberculosis (MDR-TB) has been an emerging global public health threat and area of serious concern towards efforts of global TB control. The major challenge in MDR-TB management in Tanzania is the lack of up-to-date data on adverse events (AEs) associated with MDR-TB regimens. This study aimed to determine the prevalence and factors associated with AEs among patients treated for MDR-TB at Kibong'oto Infectious Diseases Hospital (KIiDH) Kilimanjaro, Tanzania.

Methods: This was a hospital-based retrospective cross-sectional study whereby patient information was collected from patient files using a structured data extraction tool. Data from patients treated for MDR-TB at KIDH in Kilimanjaro, Tanzania from 2009 to 2019 were used for analysis. Patients with incomplete data were excluded from analysis. Adverse events were recorded either as documented by the physician or by comparing baseline laboratory results against ensuing results after initiating treatment. AE severity was graded according to the Common Terminology Criteria for Adverse Events.

Results: A total of 260 patients were analyzed. Adverse events were recorded among 87.7% of the study population with a wide spectrum of these adverse events. Most common AEs included hepatotoxicity (40.4%), nephrotoxicity (37.7%), anaemia (24.2%) and death (10%). Patients previously treated for drug susceptible tuberculosis (DS-TB) had 2.75(95%CI: 1.20–6.29; *p*=0.017) times higher odds of developing AEs compared to those never treated for DS-TB. Predictors of death were: HIV co-infection (adjusted odds ratio (AOR) 3.3, 95%CI: 1.40-7.74, *p*=0.006); and patients with a low body mass index (BMI) <18.5kg/M^2. A shorter MDR-TB regimen (AOR 2.4, 95%CI: 1.03-5.73; *p*=0.04) was a predictor of death as an AE.

Conclusion: MDR-TB patients on treatment present with a high proportion of AEs. Patients with HIV co-infection, history of previous DS-TB treatment, those with a BMI <18.5kg/M^2 and patients placed on shorter regimes are at an increased risk of developing AEs. Low BMI, HIV co-infection and use of the shorter MDR-TB regimen are associated with increased odds of dying among patients treated for MDR-TB. Therefore, it is pertinent to strengthen continuous follow-up among patients presenting with significant predictors of AEs.

Keywords: MDR-TB, tuberculosis, Tanzania, adverse events (AEs)

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Background

Multidrug-resistant tuberculosis (MDR-TB) has been an emerging global public health threat and area of serious concern to the global efforts of the tuberculosis (TB) control initiative. The world health organization (WHO) report of 2021 shows a significant decline in the total number of TB case notifications per year between 2019 and 2020, falling by 18% (7.1 million to 5.8 million) (WHO-Report, 2021). This drop could be attributed to the COVID19 Pandemic. Among the countries listed as the 30 high TB burden countries, the United Republic of Tanzania is included, however, Tanzania does not appear in the list with a high burden of MDR-TB (WHO, 2021). Based on the 2017/2018 national drug resistance survey, the overall prevalence of MDR-TB was 1.2%; this nonetheless does not dismiss the fact that MDR/RR-TB is still a growing issue (NTLP, 2019). The number of MDR-TB cases identified in Tanzania increased from 143 cases in 2014 to 167 in 2017 (NTLP, 2019).

Tanzanian treatment guidelines recommend the use of pharmacological treatment of MDR-TB using the long regimen, short regimen or the individualized regimen which was adopted from the WHO guideline (NTLP, 2020; WHO, 2020). The drugs used in the long regimen include one injectable aminoglycoside, levofloxacin, pyrazinamide, ethionamide and cylocerine (WHO, 2020). The standardized short MDR-TB regimen includes drugs such aminoglycosides and moxifloxacin, pyrazinamide, prothionamide, clofazimine, high dose isoniazid; and ethambutol (WHO, 2020). Individualized regimens may include bedaquiline, delamanid, levofloxacin, kanamycin or amikacin or capromycine, prothionamide or ethionamide, linezolid, clofazimine, cycloserine, pyrazinamide, ethambutol, isoniazid and *Para*-Amino salicylic acid (WHO, 2020).

The longer and more complex second line treatment of MDR/RR-TB is, potentially more toxic and often associated with occurrence of adverse events compared to treatment for drug susceptible TB (DS-TB) (Dela, Tank, Singh, & Piparva, 2017; Satti et al., 2012; Schnippel et al., 2016). These adverse events have a wide spectrum from mild transient adverse effects to more severe and potentially life-threatening events (Brust et al., 2013; Reuter et al., 2017). These adverse events have been shown to affect treatment such as patients requiring treatment discontinuation of one or more drugs or decreased patient adherence all of which are associated with poor treatment outcomes (Dela et al., 2017).

Studies done among patients with MDR-TB and Human Immunodeficiency Virus (HIV) co-infection were associated with varying frequencies and severity of adverse events (AEs) (Matono et al., 2017; Sogebi, Adefuye, Adebola, Oladeji, & Adedeji, 2017). Some reported risk factors for AEs are patients above 40 years of age and individuals with lower body mass index (BMI) (Chung-Delgado et al., 2011; Farazi, Sofian, Jabbariasl, & Keshavarz, 2014; Merid et al., 2019), these were more likely to experience AEs due to MDR-TB treatment (Piparva, Jansari, & Singh, 2018).

The major challenge in MDR-TB management in Tanzania is the lack of up-to-date data on the AEs associated with MDR-TB regimens. Bedaquiline was introduced in November 2015 as a part of the longer regimen, and at Kibong'oto Infectious Disease Hospital (KIDH) the shorter regimen for MDR-TB management was introduced in January 2018. There is less information regarding the safety profile of bedaquiline and the shorter regimen in the Tanzanian population. Early and proper documentation, assessment and management of the various AEs are important components of patient care towards the improvement of treatment outcomes. This study aimed at shedding more light on the safety profile and factors that may have an effect on AEs among patients treated with the different MDR-TB regimens currently used in the Tanzanian population.

Methods

Study Design

This was a hospital-based retrospective cross-sectional study whereby patient information was collected from the patient file using a specially designed data extraction form. The study involved reviewing files of patients being treated for MDR-TB attending KIDH from January 2009 to January 2019. All patients who had been treated for MDR-TB at KIDH for at least four months were included.

Files with incomplete data were excluded. Files that had missing MDR-TB card or MDR-TB card which had not been filled were considered incomplete and therefore excluded

Study Site and sample size

The study was conducted at KIDH located in the northern part of Tanzania and formerly known as Kibong'oto National Tuberculosis Hospital. The hospital was established in 1926 as a TB sanatorium. At present, KIDH is Tanzania's MDR-TB centre of excellence for MDR-TB management of patients using institutionalized care for the intensive phase followed by ambulatory treatment in their respective districts, at the nearest health facility. Currently KIDH provides TB treatment under Direct Observed Treatment (DOT) to all its patients providing choices to patients of whether to peruse home-based DOT or health facility DOT. Previously, KIDH was the sole centre providing MDR-TB services in the country until 2015 when MDR-TB treatment was decentralized. The centre of excellence works closely with other health facilities in the Kilimanjaro region to conduct community education, sensitization, and TB screening programs. All patient files that were found to be eligible based on inclusion and exclusion criteria were reviewed.

Data collection procedures

This was done by a research team comprising of clinicians, nurses, pharmacists and statisticians using the data extraction tool, after obtaining ethical clearance and hospital permission. The data extraction tool consisted of a section that collected socio-demographic data (age, height and sex), clinical risk factors for developing AEs due to MDR-TB treatment such as date of diagnosis, date of treatment initiation, HIV status, previous treatment to drug-susceptible TB, development of any type of AE. Finally, the data extraction form had a section with laboratory results including baseline and laboratory parameters up to six months after treatment initiation. Information on the socio-demographic, clinical and reports of AEs associated with MDR-TB therapy was extracted retrospectively from patient files. Collected data were entered into a password secured computer using Carstensen B, Plummer M, Laara E, Hills M (2022). *Epi: A Package for Statistical Analysis in Epidemiology*. R package version 2.47, https://CRAN.R-project.org/package=Epi.

Data analysis

The AEs were recorded as reported in the MDR-TB card, excluding the patients with abnormal laboratory values or result before beginning the MDR-TB treatment (baseline laboratory results). Patients who reported clinical AEs with no laboratory reports had their symptoms recorded, and this information was extracted as documented by the physician in the MDR-TB patient card. The criteria for determining the severity of AEs due to MDR-TB treatment was done according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 from U.S. Department of Health and Human Services National Institutes of Health and National Cancer Institute Published: Nov 27, 2017 (CTCAE, 2017). Data were coded, tabulated and statistically analyzed according to the specific objectives of the Statistical Package for Social Science- program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Frequency tables were used to summarize categorical variables and medians with interquartile ranges (IQR) or means with standard deviations (SD) were used to summarize continuous data depending on the distribution. Chi-square tests and Fisher's exact tests were used to compare the differences between proportions and a *p–value* of <0.05 was considered significant. Univariate and multivariate analysis of AEs and death using logistic regression analysis was done. The strength of association was calculated using odds ratios (OR) and 95% confidence intervals (95 % CI).

Ethical approval and consent to participate

Ethical approval was obtained from the Muhimbili University of Health and Allied Sciences (MUHAS) Ethical Review Committee before the conduct of the study. Permission to conduct the study was sought from Kibong'oto Infectious Diseases Hospital. The information obtained during the study was kept strictly confidential.

Results

A total of 340 patient files were reviewed, of which 260 were included in the study and used for analysis. Among the study population 70% were male (Table 1). Most (88.5%) of the patients were aged between 18 and 65 years, with a median age of 40 years (IQR=19). A third of the patients (37%) were found to be co-infected with HIV. More than half of the patients (57.3%) were underweight based on their BMI (BMI<18kg/M^2). The median BMI was found to be 18.9kg/M^2 (IQR=3.65). Two thirds (68.5%) of the patients were initiated on the long MDR-TB treatment regimen. A little over half (54.6%) had been previously treated for DS-TB. Among the total patients treated for MDR-TB, 87.7% developed at least one AE during the course of MDR-TB treatment.

Table 1: Social demographic characteristics of patients treated for MDR-TB at KIDH (N=260)

Categories	N (%)	Adverse Drug Reaction	
		No (%)	Yes (%)
Sex			
Female	182 (70)	7 (9)	71 (91)
Male	78 (30)	25 (13.7)	157 (86.2)
Age (in years)			
Children (<18 years)	10 (3.8)	2 (28.5)	5 (71.4)
Adults (18 to 64)	230 (88.5)	28 (12.0)	205 (88)
Elderly (>65 years)	20 (7.7)	2 (10)	18 (90)
HIV Status			
Negative	166 (63.1)	23 (13.9)	143 (86.1)
Positive	94 (36.9)	9 (9.6)	85 (90.4)
Drug Regimen			
Longer	178 (68.5)	20 (11.2)	158 (88.8)
Shorter	82 (31.5)	12 (14.60)	70 (85.3)
BMI(kg/m^2)			
Normal(18.5-24.9)	99 (38.1)	16 (16.2)	83 (83.8)
Over weight(≥25)	12 (4.6)	2 (16.7)	10 (83.3)
Under weight(<18.5)	149 (57.3)	14(9.5)	134 (90.5)
Bedaquiline			
Yes	67 (25.8)	7 (10.5)	60 (89.6)
No	193 (74.2)	25 (13)	168 (87.1)
Diabetic			
Yes	11 (4.2)	2 (18.2)	9 (81.8)
No	248 (95.4)	29 (11.7)	219 (88.3)
Previous DS TB treatment			
Yes	142 (54.6)	11 (7.8)	131 (92.3)
No	118 (45.4)	21 (18)	96 (82.1)

Key: HIV – Human immunodeficiency virus; BMI – body mass index; DS-TB – drug susceptible tuberculosis

The spectrum of AEs was found to be wide with most patients (56%) having mild to moderate AEs, 17% were severe cases and a further 15% having serious adverse events (SAE). Figure 1

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SEVERITY OF AEs

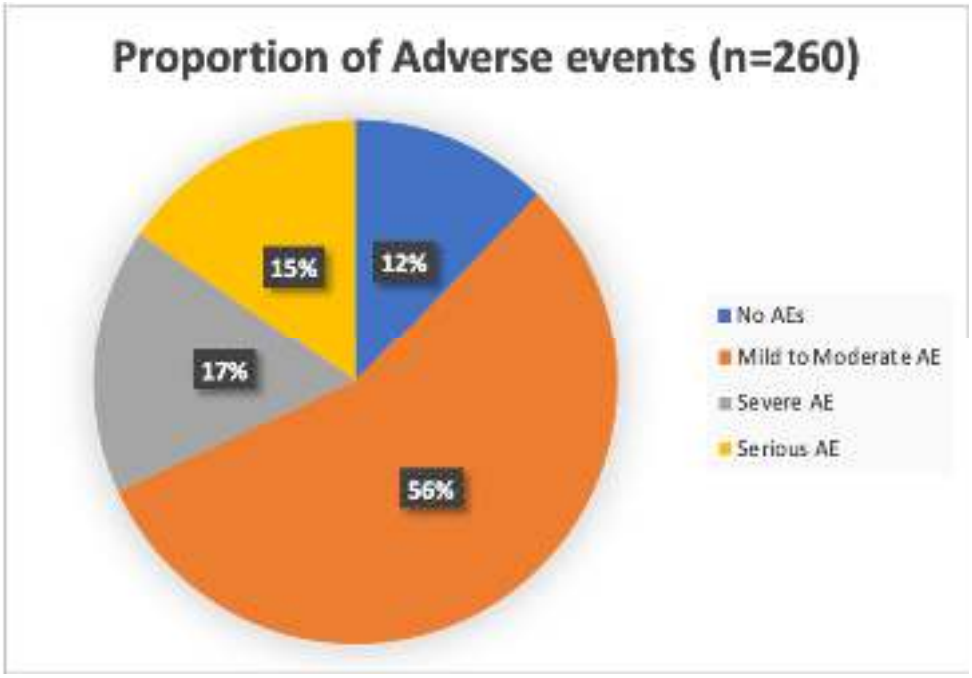

Figure 1: Proportion of adverse events among patients treated for MDR-TB

Prevalence of patients with AEs among patients treated for MDR-TB from 2009 to 2019

The prevalence of AEs among patients treated for MDR-TB was found to be 87.7%. The spectrum of the AEs associated with MDR-TB was found to be very wide. MDR-TB treatment was associated with a variety of AEs (Table 2). Most common AEs included hepatotoxicity (40.4%), nephrotoxicity (37.7%) and anaemia (24.2%).

Table 2: Proportions of patients being treated for MDR-TB having adverse events and their severity grading

Adverse Event	Patients with AE (N)	AE Severity grade			
		Mild (%)	Moderate (%)	Severe (%)	SAE (%)
Hepatotoxicity	106	92 (86.8)	9 (8.5)	5 (4.7)	0
Nephrotoxicity	98	59 (60.2)	23 (23.5)	6 (6.1)	10 (10.2)
Anaemia	62	23 (37.1)	25 (40.3)	14 (22.6)	0
Ototoxicity	54	18 (33.3)	14 (25.9)	21 (38.9)	1 (1.9)
QTcf Prolongation	36	27 (75)	8 (22.2)	1 (2.8)	0
GIT disturbance	23	11 (47.8)	8 (34.8)	4 (17.4)	0
Hypercalcemia	22	10 (45.5)	5 (22.7)	2 (9.1)	5 (22.7)
Peripheral neuropathy	16	5 (31.3)	10 (62.5)	1 (6.2)	0

Key: AE – adverse event; SAE – Serious Adverse Event; GIT – gastrointestinal tract,

Hepatotoxicity was the major AEs reported among the MDR-TB-treated patients. Of all the the106 patients that had hepatotoxicity, the majority (94.4%) were found to have mild to moderate elevation of liver enzymes namely alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with only 5.6% of the patients having severe hepatotoxicity (>5 times the upper limit of normal i.e. >200IU/L). A total of 98 (37.7%) patients had renal impairment based on the calculated estimated glomerular filtration rate (eGFR) using the Cockcroft gault equation. Most of the

patients (83.7%) had mild to moderate renal impairment, with 10.2% having life-threatening renal impairment where the eGFR was <15mL/min/1.73m^2.
A total of 70 patients had audiometry done, whereby the results showed that 54 patients (77%) were found to have ototoxicity (presenting with ≥25 decibels (dB) whereas 21 patients were found to have severe hearing loss (>80dB). Thirty-one cases (57.4%) with ototoxicity were recorded in the first month after initiation of MDR-TB treatment and 12 cases (22.2%) were recorded in the second month of treatment indicating immediate ototoxicity of the MDR-TB drugs used. 63 patients developed anaemia during the study period. At treatment initiation, the patients had a baseline median haemoglobin (Hb) level of 12g/dL (IQR=5.3) which significantly decreased to a median Hb of 9.8g/dL (IQR=3.2) during MDR-TB treatment (p<0.001, Wilcoxon log-rank test).
Electrocardiography (ECG) was performed among 143 patients. Of these, 36 patients (25.2%) had QTcf prolongation. Among patients with QTcf prolongation, 21.7% were on a bedaquiline containing MDR-TB regimen compared to 27.7% who also had QTcf prolongation but were not on a bedaquiline containing MDR-TB regimen (p=0.41). Of the patients that were found to have hypercalcemia, 22.7% had a severe elevation of serum calcium levels (>3.5mmol/L). Several patients (8.8%) also reported gastrointestinal symptoms such as nausea, vomiting and diarrhoea; however, these symptoms were mild to moderate. Table 2 shows all the proportions of patients who reported AEs together with the severity grading of these AEs.

Univariate and multivariate analysis was done to determine predictors of AEs among patients using MDR-TB treatment (Table 3). In the univariate analysis, the most significant predictor for AEs was found to be previous treatment with DS-TB (p = 0.016). All factors in the univariate analysis were included in the multivariate analysis model as being statistically significant or having known clinically significant associations. Compared to patients who were not previously treated for DS-TB, patients who were previously treated for DS-TB had about 3 times increased odds of developing AEs, (OR = 2.75, 95% CI 1.20 – 6.29, p=0.017). Though not significant, there was a trend towards patients with BMI equal or higher than 18.5kg/m^2 have 0.49 lower odds of developing AEs as compared to the patients with BMI below 18.5kg/m^2 (p<0.071).

Table3: Univariate and multivariate analysis for risk factors of AEs among patients treated for MDR-TB

		Univariate analysis			Multivariate analysis		
Variable	**Categories**	**cOR**	**95% CI**	**P - value**	**aOR**	**95% CI**	**P - value**
Sex	Male	0.62	0.26 – 1.50	0.288	0.56	0.22 – 1.43	0.224
	Female	Ref					
Age (years)	≥ 40	1.49	0.70 -3.15	0.301	1.81	0.81 – 4.02	0.147
	< 40	Ref					
BMI	≥18.5kg/M^2	0.54	0.26 – 1.14	0.106	0.49	0.22 – 1.06	0.071
	<18.5kg/M^2	Ref					
Bedaquiline	Yes	1.28	0.52 – 3.10	0.591	1.32	0.52 – 3.29	0.570
	No	Ref					
HIV infection	Yes	1.52	0.67 – 3.44	0.315	1.50	0.64 – 3.51	0.351
	No	Ref					
Treated DS-TB	Yes	2.61	1.20 – 5.66	0.016	2.75	1.20 – 6.29	0.017
	No	Ref					
Regimen	Shorter	0.74	0.34 – 1.59	0.440	0.94	0.41 – 2.15	0.883
	Longer	Ref					

Key: Bedaquiline stands for MDR-TB regimen containing Bedaquiline;
DS-TB – drug susceptible tuberculosis; MDR-TB – Multidrug resistant tuberculosis; BMI – body mass index; HIV – human immunodeficiency virus; cOR- Crude Odds Ratio; aOR- adjusted Odds Ratio; CI - Confidence Interval

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A total of 26 patients died (10%) with a median time to death being 14.5 days (IQR=48) ranging from 2 - 225 days. Kaplan-Meier analysis among these patients on the probability of death shows that the probability of death among those MDR-TB patients with HIV co-infection was statistically higher compared to MDR-TB patients who were HIV negative (p = 0.007) (Figure 1). Univariate analysis for predictors of death showed that the significant predictors were low BMI, HIV co-infection and use of the shorter MDR-TB regimen (p<0.05). Multivariate analysis showed that compared to underweight patients (BMI<18.5 kg/M^2), patients who were not underweight (BMI ≥18,5kg/M^2) had a 62% decreased chance of dying (OR = 0.38, 95%CI: 0.15-0.96, p=0.042). Patients co-infected with HIV had 3 times increased odds of dying, (OR= 3.3, 95%CI: 1.40-7.74, p=0.006). Analysis also showed that patients on the shorter MDT-TB regimen had higher odds of dying compared to those on the longer regimen (OR=2.4, 95%CI:1.03-5.73; p=0.04). Though not significant, there was a trend towards older patients (>40years of age) having a higher probability of dying as compared to younger patients (OR = 1.99, 95%CI: 0.95-5.54, p=0.06) (Table 4).

Table 4: Logistic regression analysis for factors associated with Death among patients treated for MDR-TB

		Univariate analysis			Multivariate analysis		
Variable	**Categories**	**cOR**	**95% CI**	**P – value**	**aOR**	**95% CI**	**P - value**
Sex	Male	1.08	0.45-2.57	0.861	1.13	2.89 - 6.44-	0.800
	Female	Ref					
Age (years)	≥ 40	1.99	0.88-4.50	0.096	2.26	0.95-5.54	0.064
	< 40	Ref					
BMI	≥18.5kg/M^2	0.41	0.17-1.00	0.049	0.38	0.15-0.96	0.042
	<18.5kg/M^2	Ref					
Bedaquiline	Yes	1.17	0.49-2.80	0.720	1.23	0.49-3.11	0.660
	No	Ref					
HIV infection	Yes	3.11	1.39-7.0	0.006	3.30	1.40-7.74	0.006
	No	Ref					
Treated DS-TB	Yes	0.80	0.37-1.76	0.587	1.14	0.48-2.70	0.769
	No	Ref					
Regimen	Shorter	2.41	1.09-5.33	0.03	2.42	1.03-5.73	0.04
	Longer	Ref					

Key: Bedaquiline stands for MDR-TB regimen containing Bedaquiline; DS-TB – drug susceptible tuberculosis; MDR-TB – Multidrug resistant tuberculosis; BMI – body mass index; HIV – human immunodeficiency virus; cOR - Crude Odds Ratio; aOR - adjusted Odds Ratio; CI - Confidence Interval

Kaplan-Meier graph for HIV status shows that the probability of death for those with HIV co-infection among the MDR-TB treated patients **was statistically** higher compared to MDR-TB patients with HIV negative status (Figure) (p = 0.007). Figure 2

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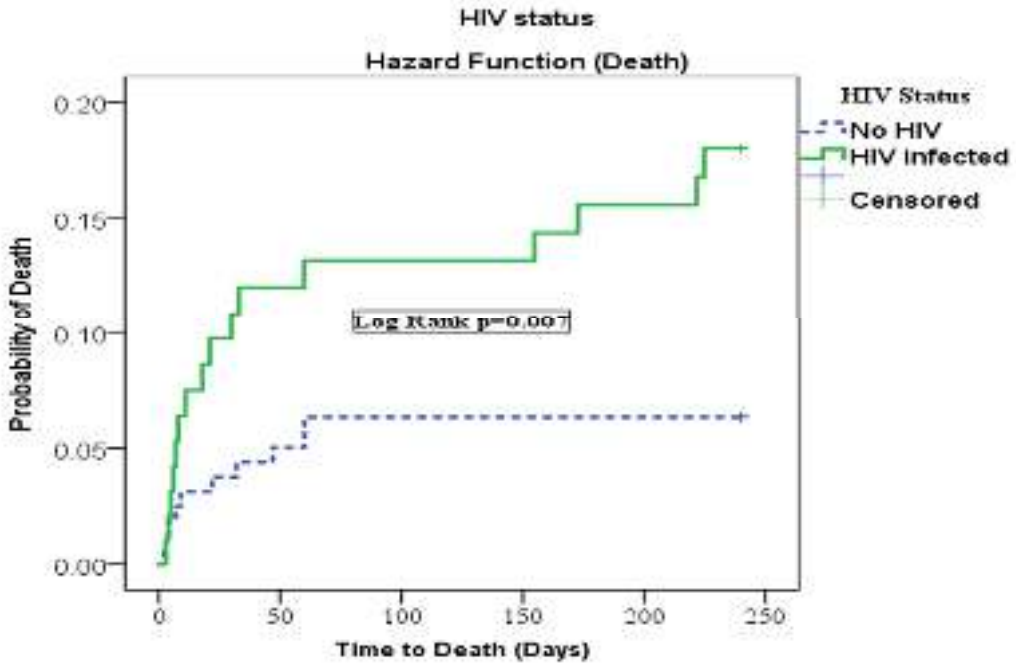

Figure 2 Kaplan Meier graph showing probability of dying for patient with HIV co-infection on MDR-TB treatment

Discussion

This study looked into the prevalence, spectrum of severity and factors associated with AEs among patients on treatment for MDR-TB. Prevalence of AEs in our study was found to be 87.7%. Most commonly reported AEs in this study include hepatotoxicity, nephrotoxicity, anaemia, ototoxicity, QTcf prolongation and death. Among patients reported with AEs, majority had mild to moderate grades of AEs with 17.5% reporting serious adverse events. Risk factors for development of AEs among these patients was found among patients previously diagnosed and treated for TB and a trend towards those with a lower BMI (<18.5kg/M^2). Factors significantly associated with death include HIV co-infection, low BMI and using the shorter MDR-TB regimen.

Prevalence of AEs associated with MDR-TB treatment at KIDH for the period of 2009-2019 was slightly higher than the 80% prevalence reported at KIDH between 2009-2011 and the 79% prevalence reported by Bloss *et al* in Latvia (Bloss et al., 2010). However, a study by Kumari *et al* reports a similar prevalence (87%) among patients on MDR-TB treatment in rural India (Kumari, 2018). Also, introduction of the shorter MDR-TB regimen in 2015 may have contributed to the higher prevalence of AEs in this study compared to the study done in KIDH by Mpagama *et al* (Mpagama et al., 2013). In India, Nagpal *et al* reported a prevalence of 92% for AEs associated with MDR-TB treatment whereas Zhang *et al* reported a prevalence of 90.7% from a Chinese cohort (Nagpal, 2018; Zhang et al., 2017). High prevalence of AEs among patients treated for MDR-TB has been attributed to the large number of drugs being used over a long period of time to ensure complete elimination of the mycobacterium tuberculosis.

Wide spectrum of the AEs was observed including hepatotoxicity, nephrotoxicity, anaemia, ototoxicity, QTcf prolongation, GIT disturbance and hypercalcaemia. The most commonly observed AE in our study population was hepatotoxicity (40.4%). This is much higher compared to studies done by Mohamed et al in Egypt, Ngoc *et al* in Vietnam and Yang *et al* from South Korea who reported 9.3%, 5.8% and 3.9% respectively (El-Din, Halim, & El-Tantawy, 2015; Ngoc et al., 2021; Yang et al., 2017). It is possible that TB itself can result in abnormal liver function by its mere

invasion of the liver through its disease process. The symptoms and signs of drug-induced hepatotoxicity can be highly variable, ranging from being asymptomatic despite elevation of liver enzymes to fulminant hepatic failure. Unlike most reported studies, GI symptoms were not the most commonly reported AE, however, 8.8% of our study population reported GI symptoms, nearly similar to those reported by Hoa *et al* (Hoa, Nhung, Khanh, Hai, & Quyen, 2015; Nathanson et al., 2004; Shin et al., 2007).

Ototoxicity was observed in 20 % of the patients in our study. This is lower compared to the 42% that was reported by Törün *et al* from a study done in Turkey, or the nearly 70% incidence that was reported by Modongo *et al* (Modongo et al., 2014; Torun et al., 2005). Hearing loss has been attributed to aminoglycosides as they are known to cause irreversible high frequency hearing loss by initially destroying the outer hair cells and moving in to the inner hair cells of the cochlea (Harris et al., 2012; Selimoglu, 2007). Our study showed a moderate prolongation of the QTc intervals reported in 13.8% of the patient population. A number of drugs used in the treatment of MDR-TB in our study could attribute to QT prolongation such as the use of bedaquiline, clofazimine and fluoroquinolone antibiotics. Bedaquline in Tanzania was only introduced in November 2015 (Lyakurwa et al., 2019). Therefore, fewer patients in this study were on MDR-TB regimen containing bedaquiline. We did not find a difference in QTcf prolongation between patients using bedaquiline and those not on a bedaquiline MDR-TB regimen.

In this study, nephrotoxicity was reported at 37.7% based on eGFR measurements. This finding could be due to active monitoring that was done by measuring serum creatinine levels at baseline and monthly thereafter. The prevalence of nephrotoxicity has a wide range from 54% in a study by Buziashvili *et al* to 4% reported by Wu *et al* (Buziashvili et al., 2019; Wu et al., 2016). The differences could be due to different definitions of renal impairment based on various defining criteria. Our study used the CTCAE staging based on eGFR whereas the study by Buziashvili *et al* used the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification of acute kidney injury (AKI).The mechanisms of aminoglycoside-induced nephrotoxicity have already been well described (Perazella, 2019).

Another finding from our study shows that the risk factors for developing AEs in our study population was previous treatment for DS-TB with a trend towards patients who have low BMI. Chung-Delgado *et al* found that the number of previous episodes of TB was also associated with poor treatment outcomes (Chung-Delgado, Guillen-Bravo, Revilla-Montag, & Bernabe-Ortiz, 2015). This was attributed to the fact that patients with previous TB were difficult to manage, and potentially on treatment for longer, and hence this longer exposure to anti-TB drugs potentially causing toxicity and greater incidence of adverse effects. Ketema *et al* and Alemu *et al* also reported that previous treatment for DS-TB was one among the significant predictors of poor treatment outcome including occurrence of AEs (Alemu, Bitew, & Worku, 2020; Ketema, Muchie, & Andargie, 2019). A number of literatures has shown that low BMI is significantly associated with a higher likelihood of AEs and adverse MDR-TB treatment outcomes (Caminero, 2010; Kamara et al., 2022). Though not significantly associated, our study also found a trend showing the patients with low BMI had a much higher risk of developing AEs compared to those with higher indices.

High mortality rates are observed globally due to MDT-TB with a number of factors attributed to these high mortality rates (Alemu et al., 2020; Bei et al., 2018; Kanwal, Akhtar, & Ahmed, 2017). Our study reported a 10% mortality, which is lower compared to the 39% mortality reported by Chingonzoh *et al* from South Africa yet higher than the 5% reported by Chung-Delgado *et al* from Peru (Chingonzoh et al., 2018; Chung-Delgado et al., 2015). HIV-coinfection was one among the factors significantly associated with mortality in our study patients. HIV infection has been previously described by many to be independently associated with mortality and poor treatment outcomes with this effect increasing with advancing HIV disease (Bei et al., 2018; Gandhi et al., 2012; Kamara et al., 2022; Kanwal et al., 2017; Trebucq et al., 2018). We have also observed an unexplained increased risk of death associated with the shorter MDR-TB treatment regimen. This

is similar to another study done in Tanzania by Myemba *et al* who reported a higher mortality rate among patients initiated on shorter MDR-TB regimen (Myemba et al., 2020). Myemba *et al* stipulated that the higher mortality rates in the shorter regimen could be as a result of many drugs (at least 7 drug combinations) used at their full dose for a short duration of time resulting in higher probability of AEs and non-compliance. Similar higher rates of mortality with the shorter regimen are reported by Abidi *et al* (Abidi et al., 2020). Our study also found a trend of higher risk of death among older patients (>45years) compared to younger patients. Older age is commonly associated with increased risk of mortality due to atypical TB presentations, more co morbidities and more frequent AEs (Loveday, Mzobe, Pillay, & Barron, 2019).

Conclusion

Treatment for MDR-TB has a wide spectrum of AEs and a significant proportion of patients experience serious adverse events. Previous treatment for DS-TB and being underweight increases the probability of developing AEs during MDR-TB treatment. Low BMI, HIV co-infection and use of the shorter MDR-TB regimen are associated with increased odds of dying among patients treated for MDR-TB**.**

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests

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Authors' contributions

AIS, SFM and GS were involved in study conceptualization, methodology, data processing, formal analysis and project administration. AIS, and HV were involved in data collection. AIS visualized and wrote the original manuscript. DL, SM, PGS and SFM supervised, reviewed and edited the manuscript. All authors read and approved the final version of this article.

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