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Adverse drug reactions and associated factors in multidrug-resistant tuberculosis: A retrospective review of patient medical records at Mbarara Regional Referral Hospital, Uganda

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Abstract

Objectives: The World Health Organization pragmatic guidelines recommend shorter duration drug regimens with newer, more efficacious agents for treatment of multidrug-resistant tuberculosis. However, adverse drug reactions associated with the use of newer, second-line agents may pose a major barrier to adequate management of multidrug-resistant tuberculosis. We therefore sought to investigate the prevalence and factors associated with adverse drug reactions among patients with multidrug-resistant tuberculosis.

Methods: We retrospectively reviewed patient medical records at the tuberculosis treatment unit of Mbarara Regional Referral Hospital, between January 2013 and December 2020. Medical records were included in the study, if the patients were aged ⩾18 years, tested sputum positive for multidrug-resistant tuberculosis, with adequate pharmacovigilance data documented. We assessed all documented health-related patient complaints, deranged laboratory values, and clinician suspected adverse drug reactions for scientific/clinical plausibility. Adverse drug reactions were confirmed using published and manufacturer drug references materials. A multidisciplinary clinician team was involved to decide whether to exclude or include a suspected adverse drug reaction.

Results: About 6 in 10 (67.4%; 120/178) patients experienced at least one adverse drug reactions during treatment, of which 18.3%, 14.6%, and 11.4% of adverse drug reactions affected the endocrine/metabolic, otic, and musculoskeletal body systems, respectively. Majority of the adverse drug reactions were probable and had a moderate severity. There was an upward trend in adverse drug reaction incidence between 2015 and 2019. Adverse drug reaction occurrence was associated with previous adverse drug reaction history (adjusted odds ratio = 2.85 (1.08, 7.53 at 95% confidence interval)); however, patients who were underweight (adjusted odds ratio = 0.34 (0.16, 0.69 at 95% confidence interval)) and those treated with bedaquiline-based drug regimens (adjusted odds ratio = 0.2 (0.07, 0.59 at 95% confidence interval)) were less likely to experience an adverse drug reaction.

Conclusion: Majority of patients with multidrug-resistant tuberculosis experience at least adverse drug reaction during the course of treatment. The newer standard shorter duration drug regimens (9–12 months) may be associated with intolerable adverse drug reactions that hamper effective management of multidrug-resistant tuberculosis. There is need for more studies to assess the clinical adverse drug reaction burden associated with the implementation of shorter duration regimens.

Keywords

Adverse drug reactions, multidrug-resistant tuberculosis, Uganda

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Introduction

Tuberculosis (TB) is among the top 10 leading causes of death worldwide, and since 2007 it is ranked the leading cause of death from a single infectious agent.[1] Globally, there were about 11 million new TB infections and 1.3 million TB-related deaths in 2019, with Southeast Asia and Africa accounting for 44% and 25% deaths, respectively.[1] There is a high burden of TB in Uganda, with an estimated incidence of 200 per 100,000 population, and a related mortality rate of 35 per 100,000 population.[2]

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB resistant to at least rifampicin and isoniazid. The global incidence of MDR-TB is 3.3% of new TB cases, and 18% of previously treated TB cases.[1] In sub-Saharan Africa, the incidence of MDR-TB is estimated at 2.1% among new TB cases. In Uganda, incidence rate is about 1.6% of new TB cases, and 12% of previously treated TB cases.[3,4] In the context of good adherence, MDR-TB has successfully been managed using second-line drugs.[5] However, these second-line drugs tend to be toxic and their longer duration of use predisposes patients to adverse drug reactions (ADRs).[6] Until 2015, treatment of MDR-TB involved the use of more toxic and longer duration (20–22) regimens in Uganda.[7,8] However, the introduction of shorter duration (9–12 months) and more tolerable regimens has redefined clinical research and management of MDR-TB.[9,10]

The WHO defines an ADR as a response to a drug that is noxious, unintended, and occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function.[11] ADRs due to MDR-TB drugs are a major public health concern, with the estimated global prevalence higher (8%–85%) among patients receiving first-line drugs, compared to patients receiving second-line drugs (69%–96%).[12,13] In Africa, about 83% of patients receiving MDR-TB treatment experience at least one ADR in the course of treatment,[14,15] with Kenya and Ethiopia reporting 61% and 98.6% prevalence, respectively.[16,17] The most prevalent ADRs manifestation among patients receiving MDR-TB treatment include cutaneous reactions, gastrointestinal reactions, respiratory symptoms, hepatic injury, renal injury, ototoxicity, musculoskeletal disturbances, and neurologic disturbances.[6,18,19] Although most ADRs are minor and do not necessitate halting/discontinuation treatment, early recognition and prompt treatment of some severe or life-threatening ADRs may warrant modification or discontinuation of MDR-TB treatment.[12,20] In addition to the disruption of therapy in terms of compliance, ADRs are also associated with other negative outcomes including increased length of hospital stay and severe illness.[5,21]

Given the scantiness of data about ADRs among patients receiving MDR-TB treatment and changes in local patterns of TB and MDR-TB prevalence in Uganda, this study aimed to assess the prevalence, types, and factors associated with ADRs among patients receiving MDR-TB treatment at Mbarara Regional Referral Hospital (MRRH), in south-western Uganda.

Methods

Study setting

The study was conducted at the TB treatment unit of MRRH in Mbarara City, Uganda. MRRH is a 350-bed tertiary hospital and is the largest referral hospital of south-western Uganda serving up to 5 million people in its catchment area, which includes 10 districts in south-western and western Uganda, as well as borderline districts from four East African countries. The TB treatment unit is a 20-bed facility serving both susceptible and MDR-TB patients. The TB treatment unit at MRRH is among the first MDR-TB centers constructed in Uganda and has enrolled about 200 drug-resistant TB patients to date. All patients admitted to the unit are hospitalized for 2 weeks irrespective of their functional status, where they receive medication, and are actively monitored for ADRs. Clinically stable patients are then discharged and continue to receive outpatient treatment under directly observed therapy from their nearest public health facility. The treatment supporter (trained nursing officers/public health officers) at the nearest health facility documents any suspected ADR and notifies the regional center during their mentorship trainings. All ADRs are documented in a database alongside patient characteristics and treatment outcomes.

Study population

All MDR-TB patient medical records registered at the TB treatment unit of MRRH, between January 2013 and December 2020.

Eligibility criteria

This study included all patient medical records with patient age $\geqslant$18 years, sputum positive for MDR-TB, and adequately documented pharmacovigilance information.

Study design

We conducted a retrospective study between February and May 2022.

Sample size

All MDR-TB patients' medical records that fulfilled the eligibility criteria were reviewed.

Data collection procedure

Eligible patient files were reviewed by a team of clinical pharmacists, and all documented patient complaints, deranged laboratory values, and clinician-suspected ADR

Table 1. Definition of ADRs used in the study.

ADR category	Definition
Endocrine/metabolic	Measurement of thyroid stimulating hormone (TSH) greater than 5 IU/L, serum potassium/sodium level below or above the normal range
Otic	Hearing loss confirmed by audiometry, tinnitus, loss of balance
Musculoskeletal	Myalgia, joint pain, joint swelling, or back pain reported by patients and elevated uric acid
Gastrointestinal	Nausea and vomiting, epigastric pain, abdominal discomfort, diarrhea, and constipation
Central nervous system	Psychosis confirmed by a psychiatrist, seizures reported by patient or caretaker, anxiety and the presence of depression
Hepatic	Elevation of the serum transaminases greater than three times the normal upper limit Elevation of serum total bilirubin >2 times the normal upper limit
Dermatological	Patient report of skin rash, itching, or photosensitivity reaction
Peripheral nervous system	Tingling sensation in the extremities, numbness of the limbs
Renal	Elevation of at least one serum creatinine level more than 1.5 times the baseline
Ocular	Patient-reported visual changes including poor vision, loss of vision, or pain in the eyes
Hematological	Decrease in the white cell or platelet counts less than the normal lower limit or decrease in hemoglobin level
Cardiovascular	Patient report of palpitations or QT prolongation on ECG
Miscellaneous	Any other symptoms deemed an ADR by the principal investigator

ADR, adverse drug reaction.

data were aggregated and recorded in a data collection form. All suspected ADRs in this study were defined according to the WHO definition; "any response to a drug, which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy or for modification of physiologic function."[11] All ADRs caused by non-anti-TB medications were automatically excluded after comprehensive medication review.

Suspected ADRs were identified from documented patient complaints and clinician-suspected ADRs after assessment for scientific/clinical plausibility. Using online databases and published literature,[22,23] only potential ADRs that fulfilled the criteria of $\geqslant$1% incidence rates were included in the study. If an abnormal laboratory values and/or clinical investigations was documented, an ADR was only suspected if at least three consecutive measurements were abnormal after starting MDR-TB treatment, and if the baseline or recent measurements were normal/close to normal. In the case that a suspected ADR was clinically questionable or the investigators failed to agree, a team of multidisciplinary clinicians discussed until a consensus was reached, whether to exclude or include a suspected ADR.

All suspected ADRs associated with MDR-TB regimens 1, 2, and 3 were categorized based on the body system affected using the International Statistical Classification of Diseases for Mortality and Morbidity Statistics (ICD-11 MMS)[24] (Table 1). The causality and severity of the documented ADRs were determined using the Naranjo causality scale[25] and modified Hartwig and Siegel criteria,[26] respectively. We considered the longer course (20–24 months) MDR-TB regimen (6KmLfxEtoCsZ/18LfxEtoCsZ) as regimen 1, and the shorter course MDR-TB regimens (at least 9 months) as regimen 2 (4KmMfxEtoCfzZHhigh-doseE/5MfxCfzZE) and regimen 3 (9BDQ/Lzd/Lfx/Cfz/Cs).

Statistical analysis

Respective participant data were entered and analyzed using statistical software (SPSS version 23.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to determine the prevalence of ADRs and the frequencies of different categories of ADRs. The factors associated with ADRs were determined using univariate and multivariate binary logistic regression analyses and presented as odds ratios (ORs) with a 95% confidence interval (CI). All variables with a p value of <0.25 in univariate logistic regression were considered for multivariate analysis. The level of statistical significance was at the p value of <0.05.

Ethical consideration

The study proposal was approved by Research Ethics Committee (REC) of Mbarara University of Science and Technology, and a waiver of consent to use secondary data was obtained from REC (MUST-2021-194). Permission to access and use patient records was granted by the in-charge of the TB treatment unit at the MRRH. Using codes where necessary, we ensured that confidentiality of patient information was maintained during throughout the study process. The data collectors complied to the basic infection control strategies against TB and SARS-CoV-2, by donning on N-95 mask, and proper hand hygiene throughout the study period.

Results

General characteristics of the participants

A total of 178 patients' medical records included in the study (Figure 1). The majority (130, 73.0%) were males, 110 (61.8%) were less than 41 years of age (mean = 38.85; SD $\pm$ 11.82 years,)

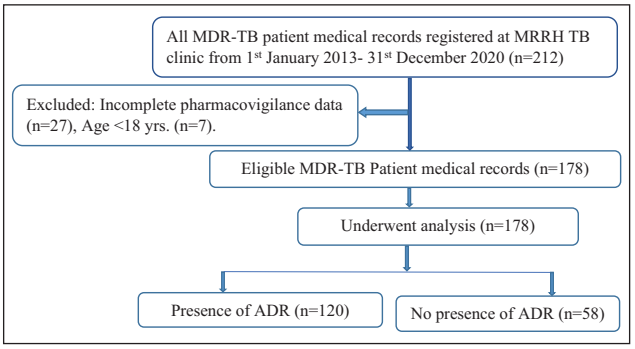

Figure 1. Study flow diagram of medical records assessed for ADRs among patients with MDR-TB at the MRRH between January 2013 and December 2020.

Table 2. Demographic characteristics of MDR-TB patients registered at MRRH between January 2013 and December 2020.

Variable	Category	Frequency	Percentage (%)
Age (years)	⩽40	110	61.8
	⩾41	68	38.2
Gender	Female	48	27.0
	Male	130	73.0
Body mass index (kg/m^2)	Underweight	73	40.4
	Normal weight	105	59.6
Marital status	Single	40	22.5
	Married	96	53.9
	Divorced/separated/ widowed	42	23.6
Education level	None	57	32.0
	Primary	63	35.4
	Secondary/tertiary	58	32.6
Alcohol use	No	54	30.3
	Yes	124	69.7
Smoking status	No	94	52.8
	Yes	84	47.2

and 105 (59.6%) had normal body mass index (BMI). More than a third (63, 35.4%) of the participants had primary education, 96 (53.9%) were married, 124 (69.7%) had a history of alcohol use, and 84 (47.2%) had a history of smoking (Table 2).

Drug and disease characteristics of the participants

Out of all the participants, 2 (1.1%) had a history of allergies, 45 (25.3%) had experienced an ADR before MDR-TB treatment was started, and 130 (73.0%) were <3 months since MDR-TB diagnosis. The majority of 116 (65.2%) participants had at least one comorbidity, 96 (53.9%) had been previously treated for TB, 101 (56.7%) received regimen 1, 93 (52.2%) received treatment for more than 9 months, and 111 (62.4%) received a total of more than five medications other than the anti-TB drugs (Table 3).

Table 3. Prevalence of drug and disease-related factors of MDR-TB patients registered at MRRH between January 2013 and December 2020.

Variable	Category	Frequency	Percentage (%)
Previous allergies	No	176	98.9
	Yes	2	1.1
Experienced an ADR before MDR-TB regimen started	No	133	74.7
	Yes	45	25.3
Duration since MDR-TB diagnosis	<3 months	130	73.0
	3–6 months	22	12.4
	>6 months	26	14.6
Comorbidities	Comorbidities other than HIV	86	48.3
	HIV	92	51.7
Treatment category	Treatment naive	82	46.1
	Previously treated	96	53.9
Treatment regimen	Regimen 1	101	56.7
	Regimen 2	51	28.7
	Regimen 3	26	14.6
Duration of treatment (months)	⩽9	85	47.8
	>9	93	52.2
Total number of drugs	<5	111	62.4
	⩾5	67	37.6

Regimen 1 (6KmLfxEtoCsZ/18LfxEtoCsZ); Regimen 2 (4KmMfxEtoCfzZHhigh-doseE/5MfxCfzZE); and Regimen 3 (9BDQ/Lzd/Lfx/Cfz/Cs).

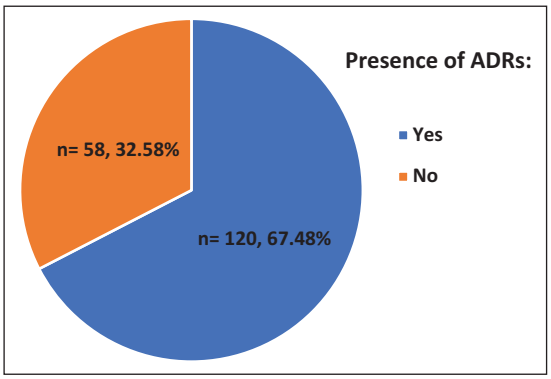

Figure 2. Prevalence of ADRs among patients with MDR-TB at MRRH between January 2013 and December 2020.

Primary outcome: Prevalence of the MDR-TB treatment-related ADRs

Out of the 178 MDR-TB patients included in the study, 120 (67.4%; 61%, 75% at 95% CI) patients experienced a total of 378 ADRs (mean = 2.12 ± 1.87 ADRs) associated with use of MDR-TB treatment. Out of 120 patients who experienced at least one ADR during the course of treatment, 75 (62.5%) experienced between one and three ADRs, while 45 (37.5%) experienced at least four ADRs (Figure 2).

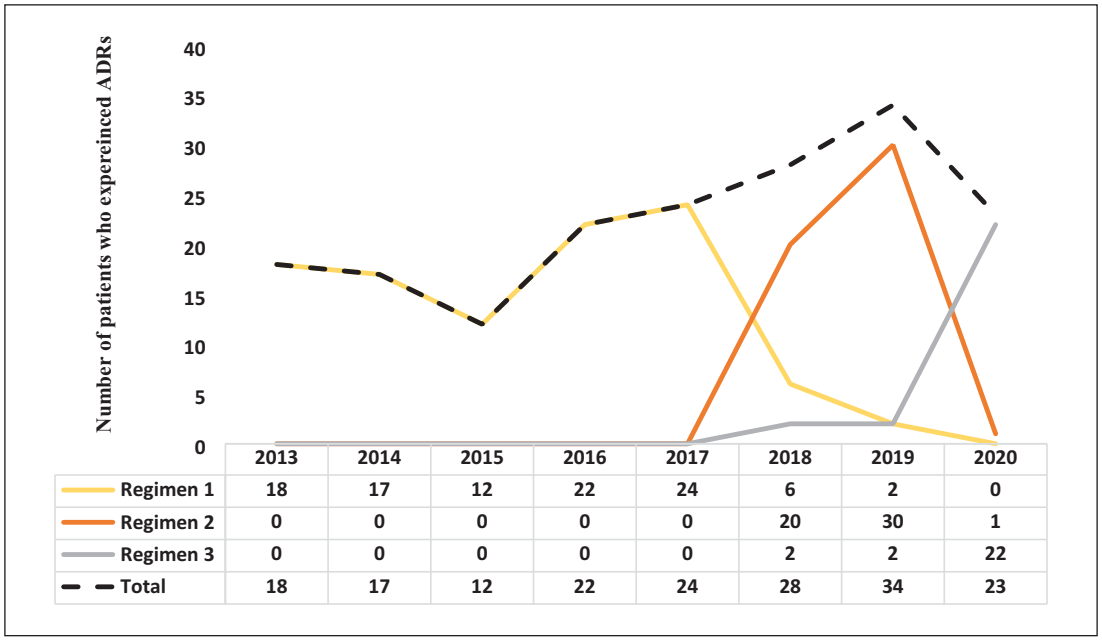

Figure 3. Number of MDR-TB patients with suspected ADRs at the TB treatment unit of MRRH, between January 2013 and December 2020.

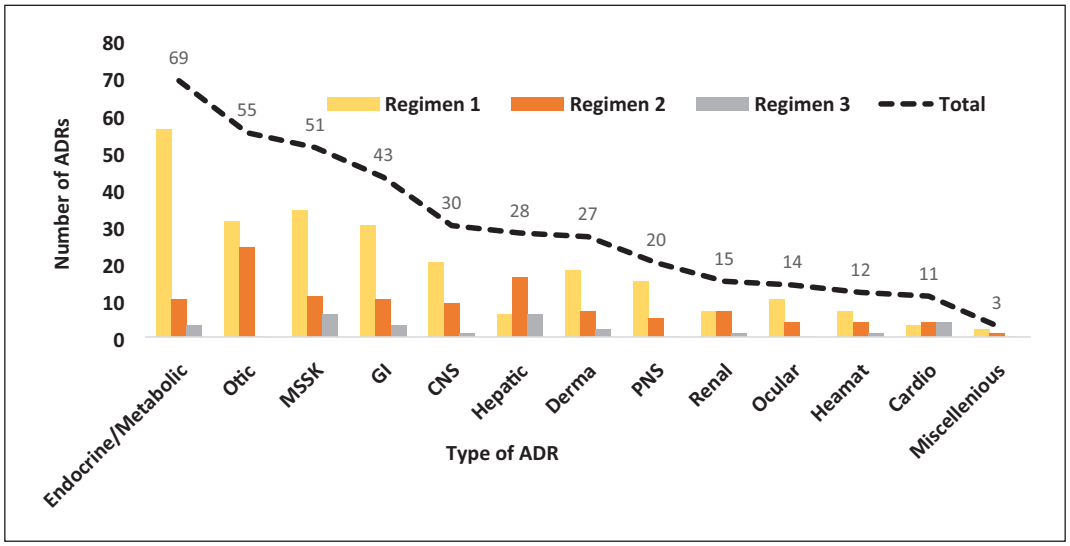

Figure 4. Number of ADRs contributed by each of the three MDR-TB treatment regimens.

Between 2013 and 2020, there was generally an upward trend in the ADR incidence. ADR incidence was highest in 2019 (34, 19.1%), compared to 2015 (12, 6.7%). Patients treated with regimen 1 consistently experienced a higher proportion of ADRs compared to other regimens (Figure 3).

Generally, endocrine/metabolic ADRs were the most experienced type of ADRs (69, 18.3%). Regimen 1 contributed the highest proportion (56, 81.2%) of all endocrine/metabolic ADRs experienced by MDR-TB patients over the 8-year duration (2013–2020) (Figure 4).

Secondary outcome: Types of ADRs among MDR-TB patients at MRRH

Out of the 378 ADRs identified, 69 (18.3%) were endocrine/metabolic, 55 (14.6%) were otic, 51(13.5%) were musculoskeletal, and 43 (11.4%) were gastrointestinal system. The five most commonly reported specific ADRs were arthralgia (44, 24.72%), hearing loss (40, 22.47%), hypothyroidism (35, 19.66%), elevated liver transaminases (27, 15.17%), and generalized body itching and rash (26, 14.61%) (Table 4).

Table 4. Types of ADRs among patients with MDR-TB at MRRH between January 2013 and December 2020.

S/N	ADR category	Frequency/percentage	Type of ADR
1	Endocrine/metabolic	69 (18.3%)	Hypothyroidism (35), electrolyte imbalance (22), gynecomastia (12)
2	Otic	55 (14.6%)	Hearing loss (40), tinnitus (15)
3	Musculoskeletal	51 (13.5%)	Arthralgia (44), back Pain (4), myalgia (2), joint swelling (1)
4	Gastrointestinal	43 (11.4%)	Epigastric pain (19), nausea and vomiting (17), gastritis (1), abdominal pain (1), bloating (1), hypersalivation (1), metallic taste (1), constipation (1), diarrhea (1)
5	Central nervous system	30 (8%)	Headache (7), insomnia (7), psychosis (6), dizziness (5), seizures (3), anxiety (1), panic attacks (1)
6	Hepatic	28 (7.4%)	Elevated transaminases (27), fulminant hepatitis (1)
7	Dermatological	27 (7.1%)	Generalized body itching and rash (26), urticaria (1)
8	Peripheral nervous system	20 (5.3%)	Tingling sensation in the limbs (9), numbness of body extremities (7), limb paralysis (3), paresthesias (1)
9	Renal	15 (4%)	Acute kidney injury (15)
10	Ocular	14 (3.7%)	Visual disturbances (14)
11	Hematological	12 (3.2%)	Thrombocytopenia (3), Anemia (3), pancytopenia (2), neutropenia (2), leucopoenia (1), lymphopenia (1)
12	Cardiovascular	11(2.9%)	Palpitations (5), QT prolongation (5), peripheral edema (1)
13	Miscellaneous	3 (0.8%)	Pain at injection site (3)

ADRs, adverse drug reactions; MDR-TB, multidrug-resistant tuberculosis; MRRH, Mbarara Regional Referral Hospital.

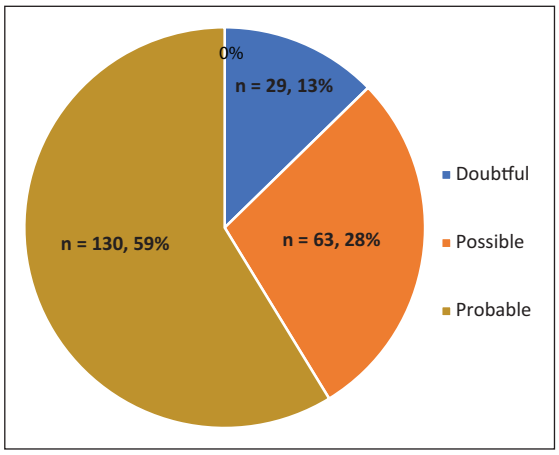

Figure 5. Naranjo causality assessment of suspected ADRs experienced by patients with MDR-TB at Mbarara regional referral between January 2013 and December 2020.

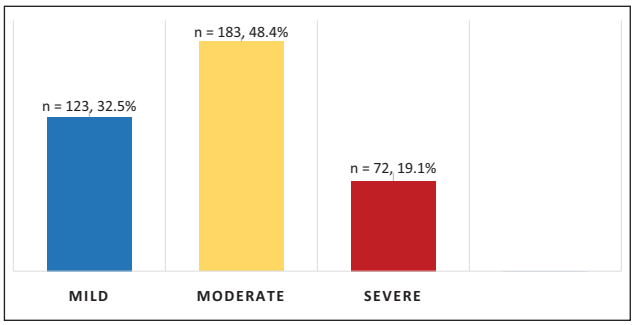

Figure 6. Hartwig and Siegel severity rating of suspected ADRs among patients with MDR-TB at MRRH between January 2013 and December 2020.

Causality and severity of suspected ADRs

Over a half (222, 58.7%) of the suspected ADRs were rated as probably related to MDR-TB treatment. Almost a half (183, 48.4%) were determined to have a moderate severity (Figures 5 and 6).

Tertiary outcome: Factors associated with ADRs among patients with MDR-TB

In univariate analysis, being under weight (crude OR (COR)=0.42 (0.22, 0.80 at 95% CI); p value=0.01), and MDR-TB treatment with the bedaquiline (BDQ)-based regimen (COR=0.31 (0.13, 0.75 at 95% CI); p value=0.01) were significantly associated with occurrence of ADRs. Five variables with a p value of <0.25, including BMI, history of ADR, treatment category, treatment regimen, and total number of drugs qualified for multivariate analysis (Table 5). In multivariate analysis, being under weight (adjusted OR (AOR)=0.34 (0.16, 0.69 at 95% CI); p value=0.003), history of ADR (AOR=2.85 (1.08, 7.53 at 95% CI); p value=0.03), and MDR-TB treatment with the BDQ-based regimen (AOR=0.2 (0.07, 0.59 at 95% CI); p value=0.004) were determined to be significantly associated with occurrence of an ADR during hospitalization (Table 5).

Discussion

This retrospective study assessed the prevalence, types, and factors associated with ADRs among 178 patients treated for DR-TB in the period between 1st January 2013 and 31st December 2020, at the TB treatment unit of

Table 5. Factors associated with ADRs among patients with MDR-TB at MRRH between January 2013 and December 2020.

Variable	Category	Presence of ADR		COR (95% CI)	*p* Value (<0.2)	AOR (95% CI)	*p* Value (<0.05)
		No	Yes				
Body mass index (kg/m^2)	<18.5	32 (43.8%)	41 (56.2%)	0.42 (0.22, 0.80)	0.01**	0.34 (0.16, 0.69)	0.003**
	⩾25	26 (24.8%)	79 (75.2%)	1		1	
	Yes	30 (35.7%)	54 (64.3%)	0.76 (0.41, 1.43)	0.40		
ADR history	No	48 (36.1%)	85 (63.9%)	1		1	
	Yes	10 (22.2%)	35 (77.8%)	1.98 (0.90, 4.34)	0.09*	2.85 (1.08, 7.53)	0.04**
Treatment category	Treatment naïve	31 (37.8%)	51 (62.2%)	1		1	
	Previously treated	27 (28.1%)	69 (71.9%)	1.55 (0.83, 2.92)	0.17*	1.14 (0.52, 2.51)	0.74
Treatment regimen	Regimen 1	30 (29.7%)	71 (70.3%)	1		1	
	Regimen 2	13 (25.5%)	38 (74.5%)	1.24 (0.58, 2.64)	0.57	1.08 (0.47, 2.5)	0.85
	Regimen 3	15 (57.7%)	11 (42.3%)	0.31 (0.13, 0.75)	0.01**	0.2 (0.07, 0.59)	0.004**
Total number of drugs	<5	41 (36.9%)	70 (63.1%)	1		1	
	⩾5	17 (25.4%)	50 (74.6%)	1.72 (0.88, 3.37)	0.11*	1.15 (0.53, 2.49)	0.72

Regimen 1 (6KmLfxEtoCsZ/18LfxEtoCsZ); Regimen 2 (4KmMfxEtoCfzZHhigh-doseE/5MfxCfzZE); and Regimen 3 (9BDQ/Lzd/Lfx/Cfz/Cs).
*Variables included in multivariate analysis.
**Statistically significant variable.

MRRH, south-western Uganda. Although there are generally standardized DR-TB treatment regimens for the general population, individualization of drug regimens is a common clinical scenario depending on concurrent medications used, actual or potential risk factors for severe disease and ADRs, albeit with little flexibility due to limited pharmacological alternatives. Although the longer duration regimens (20–24 months) are still an alternative regimen in DR-TB treatment; Over the past 16 years, the WHO has published guidelines for pragmatic DR-TB treatment, with progressive shortening of duration of use of standardized DR-TB treatment regimens, composed of newer and more toxic agents, for example, BDQ and delamanid.[7–10]

In this study, 120 patients experienced a total of 378 (mean, 2.12 ± 1.87) ADRs (Figure 2), which were predefined (Table 1). The prevalence of ADRs associated with MDR-TB treatment was 67.4% (61%, 75% at 95% CI). The prevalence of ADRs in our study setting was comparable to previous findings in Pakistan (72.4%)[20] and Indonesia (70%).[27] This can partly be explained by the fact that the pharmacovigilance systems in the two study settings are similar to our setting. On the other hand, the prevalence of ADRs in this study was generally lower than previous findings in Nigeria (99%),[28] Ethiopia (98.6%),[16] and Egypt (96.4%).[29] The prevalence in our study was comparatively higher than previous studies in India (32.4%)[30] and Eritrea (15.8%).[31] Differences in study design, definition of ADRs, and pharmacovigilance systems can explain the difference between our study finding and the studies in Ethiopia, Egypt, Ethiopia, India, and Eritrea. The studies in Nigeria and Ethiopia used a cross-sectional design unlike ours that was retrospective. In defining an ADR, our definition included only ADRs that were objectively confirmed and/or otherwise agreed upon by a team of healthcare experts, unlike studies that included all suspected ADRs. However, there is need to explore reasons that could justify the similarity between these settings. By 2015, the ADR incidence rate had declined in our study (12, 6.7%). The clinical experience of high ADR incidence associated with the 20–24 months WHO-recommended regimens[8] prompted a quick and versatile response by the pharmacovigilance systems, for example, the rollout of ADR risk stratification systems. However, the upward trend in ADR occurrence starting in 2017 (Figure 3) coincides with the period when standardized shorter duration treatment regimens with second-line drugs were rolled out for drug-resistant TB treatment in Uganda.[9,10] This finding concurs with findings from the STREAM trials, indicating the high incidence of grade 3 or higher events with the shorter course regimens compared to the 20- to 24-month regimen recommended by WHO in 2011.[32] Second, the heightened pharmacovigilance systems following the rollout of the shorter regimens in Uganda could have progressively improved the ADR detection and reporting rates. The global pandemic of COVID-19 posed a difficult to access of DR-TB treatment, especially in resource-limited settings, including the rural areas of south-western Uganda. This explains the decline in the number of ADRs documented in 2020. Generally, a higher proportion of patients on the 20–24 months MDR-TB drug regimen experienced ADRs (101, 56.7%), compared to patients on the short-course BDQ (51, 28.7%) and non-BDQ-based regimens (26, 14.6%) (Figure 4). Although the shorter regimens are known to be cost-effective (healthcare system perspective),[33] and non-inferior (albeit more toxic) compared to the long-course WHO-recommended regimens,[32] these regimens had been used for a shorter period in our settings compared to the 20- to 24-month regimen (3 years versus 8 years) at the time of the study. This could explain the less ADRs documented from

the two short-course regimens. Larger studies focusing on comparing the safety profiles of the two shorter course MDR-TB regimens are required.

Out of the 378 ADRs identified in this study, more than half were related to endocrine/metabolic (18.3%), musculoskeletal (14.6%), otic (13.5%), and gastrointestinal (11.4%) systems. Findings from the current study were comparable to those of previous studies in China,[34] Indonesia,[27] and Ethiopia[35] (Table 4). Findings from the current study show that the three commonest ADRs encountered among the 120 patients who experienced at least one ADR were arthralgia (24.7%), hearing loss (22.5%), and hypothyroidism (19.7%). Consistent with other studies conducted in Pakistan (24.3%)[20] and Indonesia (12.5%),[27] arthralgia (24.7%) was the commonest observed ADR among patients in the current study. In this study, arthralgia was diagnosed based on patient reports of joint pain and a laboratory finding of hyperuricemia at any one point during the monthly follow-ups. Arthralgia was associated with the use of pyrazinamide, which is known to reduce uric acid renal clearance by more than 80% at the therapeutic dose of 300 mg/day.[36,37] About one-fifth of the patients in our study (22.5%) experienced hearing loss, and the findings this study were comparable with previous reports in the United Kingdom (28%),[38] Pakistan (21.0%),[20] and Australia (28.3%).[39] However, the prevalence of hearing loss in this study was higher than that reported in Botswana (10%)[40] and Ethiopia (4.8%).[41] The contrast in the findings could be explained by the unavailability of audiometric assessment as is reported in the studies in Ethiopia and Botswana, which could have led to the underestimation of the ADR. In the current study, hearing loss was objectively detected by audiometry studies at patient follow-up visits. Consistent with other studies, hearing loss was associated with the use of injectable aminoglycosides-kanamycin (Km) in our setting, and often resulted in the modification of the treatment regimen to include the less ototoxic amikacin or use of alternate day Km. From the current study, the third most common ADR was hypothyroidism (19.66%) associated with the use of ethionamide, whose finding was generally lower than those in previous studies in the United Kingdom (71.4%),[42] Lesotho (69%),[43] India (54%),[44] and Australia (37%).[45] This could be explained by a possible underestimation of the ADR in this study since about 20% of the patient medical records did not have the TSH levels monitored monthly. Notably, the short-course non-BDQ-based regimen was associated with high occurrence of ototoxicity (24, 43.5%) and hepatotoxicity (16, 57.1%) in our study (Figure 4). This is consistent with reports from other highly disease-burdened settings that reported hepatotoxicity and ototoxicity as commonly experienced by TB patients on the new short-course regimens.[46,47] Further investigation is necessary to ascertain the long-term clinical safety of the shorter course regimens.

Over a half (58.7%) of the ADRs in our study were rated as probable which are consistent with those in India (51.02%)[48] and almost a half (48.4%) were determined to have a moderate severity whose findings are comparable to those in India with 50.2%.[35] In this study, ototoxicity and psychosis associated with Km and cycloserine (Cs), respectively, were the most common severe ADRs.

From the current study, patients who were underweight were 66% less likely (AOR = 0.34 (0.16, 0.69 at 95% CI); p value = 0.003) to experience an ADR. The current association of BMI<18.5 Kg/m2 with ADR occurence among DR-TB patients was comparable with the findings of previous studies in China and Pakistan (OR = 2.13; 1.17, 3.89 at 95% CI).[20,49] The possible explanation may be because doses for the anti-TB drugs are adjusted according to the patient body weight. The lower the weight, the lower the dose of the drugs received and therefore less adverse reactions. However, this explanation fails to account for non-dose-dependent ADRs. Patients who had a history of ADR were 2.85 times (AOR = 2.85 (1.08, 7.53 at 95% CI); p value = 0.03) more at risk of ADR during DR-TB treatment. These findings are comparable to those in Iran (OR = 17.46; 1.96, 20.42 at 95% CI)[50] and a systematic review in India (OR = 17.46).[51] This association may be explained by immunological reactions that tend to be worse on repeated exposure as a result of immunologic memory or cross-reaction to different drugs.[52] This can also be explained by the fact that more toxic second-line drugs are used in the DR-TB treatment that increases the risk of ADRs. Comprehensive medication-use assessment and ADR history taking, especially among patients being re-treated with anti-TBs, are paramount in reducing ADR recurrence among MDR TB patients. In addition, findings from this study revealed that patients who were treated with the BDQ-based regimen were 80% less likely to experience an ADR (AOR = 0.2 (0.07, 0.59 at 95% CI); p value = 0.004). The BDQ-based regimen is composed of BDQ, linezolid, levofloxacin, clofazimine, Cs which are given for a total of 9 months. The shorter duration of treatment period using the regimen and the lower incidence of drug–drug interactions with the individual constituents of the regimen may explain the lower ADRs with the use of the BDQ-based regimen. This is in agreement with the results of a meta-analysis by Lan et al.[53]

Limitations

Our study has definite limitations, primarily given that patient interviews, observations, and physical assessments were not conducted, the actual prevalence of ADRs over the 7 years could have been underestimated in our study. Being a smaller and single-centered study with no power calculation may also limit the validity and generalizability of our findings.

Conclusion

As DR-TB regimens evolve into shorter, more efficacious regimens, there is more need to closely evaluate the safety of these newer, shorter regimens. The challenge of ADRs may present an actual clinical challenge to effective management

of DR-TB in Uganda. Experiencing an ADR prior to MDR-TB treatment predisposes one to ADRs, whereas patients who are underweight or being treated with a BDQ-based regimen were less likely to experience an ADR.

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Author contributions

All authors contributed to the research and manuscript development equally.

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Ethical approval and consent to participate

This study was approval by the Mbarara University of Science and Technology Research and Ethics Committee (MUST–REC) Ref. No. MUST-2021-194. No consent to participate was obtained since medical records were used in the study; however, administrative clearance was obtained from the TB treatment unit of MRRH to access the records for the purpose of research.

Informed consent

Informed consent was not sought for the present study because the investigators were granted informed consent waiver from MUST REC to review patient medical records/files.

Trial registration

Not applicable.

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Availability of data and material

The data and materials of this study will be available upon request.

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