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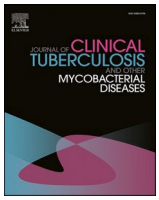

Treatment success and mortality among people with multi-drug resistant and rifampicin resistant-tuberculosis on bedaquiline-based regimen at three referral hospitals in Uganda: A retrospective analysis

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ABSTRACT

Introduction: In Uganda, people with multi-drug resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) have been treated with a bedaquiline-based regimen since 2020. Still, their treatment outcomes have not been rigorously studied. We describe the treatment outcomes of people with MDR/RR-TB treated with a bedaquiline-based regimen and analyze the factors associated with their treatment success at three referral hospitals in Uganda.

Method and materials: We retrospectively reviewed medical records for people with MDR/RR-TB treated with a bedaquiline-based regimen between January 2020 and December 2021 at 3 referral hospitals. Treatment success was defined as cure or treatment completion on a binary scale at the end of the MDR/RR-TB treatment. Factors independently associated with treatment success were analyzed using the modified Poisson regression analysis with robust standard errors, reported as risk ratio (RR) and 95% confidence interval (CI). Analyses were performed at a 5% level of statistical significance.

Results: Of 71 participants aged ≥ 15 years, 13 (18.3 %) completed treatment, 46 (64.8) were cured, 8 (11.3) died, and 4 were lost to follow-up. Overall, 59 (83.1) were successfully treated. Current alcohol consumption (adjusted RR [aRR] 0. 78, 95 % CI 0.60–0. 99) and high aspartate aminotransferase levels (aRR 0.77, 95 % CI 0.60–0.98) were associated with a lower treatment success.

Conclusion: The treatment success among people with MDR/RR-TB on a bedaquiline-based regimen was relatively high. High AST levels and alcohol consumption are associated with a lower treatment success. There is a need to strengthen psychosocial support regarding the harmful effects of alcohol consumption and its interaction with drugs, including routine monitoring of liver function to enhance the TB treatment success.

Our study is the first to describe treatment success among people with MDR/RR-TB in three large hospitals in Uganda, this provides a good picture of treatment success among people with MDR/RR-TB on bedaquiline-based regimens in the country. The weaknesses are the smaller sample size, we analyzed data spanning a relatively shorter period, and alcohol use was measured by self-reporting, this might have underestimated its association with treatment success.

1. Background

Globally, more than 10 million people fall sick of tuberculosis (TB), and about 1.4 million deaths occur annually, making TB the second deadliest cause of death from a single infectious agent [1] Estimates suggest that every 13 s, one person contracts TB globally whereas in Africa, one person dies of TB every 60 s [1]. Despite the increase in the treatment success rate, about 15 % of individuals with MDR/RR-TB die from the illness [2]. In 2022, 160,000 people died from MDR/RR-TB globally [1], and in sub-Saharan Africa a *meta*-analysis of 43 cohort

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studies revealed that the pooled incidence of mortality was 17 % [3]. Like many African countries, Uganda has a significant burden of TB, HIV, and MDR-TB [4],with MDR/RR-TB incidence of 63 (38–98)/100,000 population in 2021 [5].

In 2016, before the introduction of bedaquiline-based regimens in Uganda, there was a significant mortality of about 19 % (n = 66) when 353 people with MDR/RR-RB individuals were started on the standard treatment. This mortality was mainly observed among people with HIV-associated MDR/RR-TB (68 % or n = 45), individuals without formal education (adjusted odds ratio of 3.61), poor drug adherence (adjusted odds ratio of 1.92), and those over 50 years old (adjusted odds ratio of 3.04) [6]. With findings from randomized trials showing better cure rates and shortened treatment duration among participants on an all-oral bedaqualine-based regimen [7,8], in 2019, the World Health Organization (WHO) recommended using an all-oral bedaqualine-based regimen for treating all people with MDR/RR-TB [9]. Evidence from cohort studies and a *meta*-analysis show that people on bedaquiline-based regimens have a lower risk of death, high culture conversion rates, and better treatment outcomes when compared to those on older injectable MDR/RR-TB treatment regimens [10–12].

In Uganda, more than 95 % of people with MDR/RR-TB have been treated with a bedaquiline-based regimen since it became available in 2020 but their treatment outcomes have not been rigorously studied. Understanding the treatment outcomes among people with MDR/RR-TB on bedaquiline-based regimens in Uganda will help guide the National TB Control Program, healthcare providers, and policymakers regarding regimen performance in real-world settings, including designing measures to optimize the treatment outcomes. Accordingly, we describe treatment outcomes among people with MDR/RR-TB treated with a bedaquiline-based regimen and analyze the factors associated with treatment success at three referral hospitals in Uganda.

2. Methods and materials

Data source.

The data analyzed are from a retrospective review of medical records for people with MDR/RR-TB who had received a bedaquiline-based regimen between January 2020 and December 2021 at three referral hospitals, namely the Mbarara, Mulago, and Masaka. All three referral sites have a drug-resistant TB (DR-TB) clinic that uses the same data collection and reporting health management information system. We retrieved all available records and examined them for accuracy, completeness, and consistency through data validation with the health workers at the DR-TB clinic. Sociodemographic, clinical, and laboratory data were abstracted from participants aged ≥ 15 years. We excluded records for people with pre-extensive drug resistant tuberculosis (pre-XDR) as they were treated with a different regimen. The Mbarara University of Science and Technology Faculty Review Committee approved the study (MUST-2022–443). The need for informed consent was waived by the ethics committee based on existing rules and guidelines since it would be difficult to trace the participants. Unique codes were used to maintain participant privacy and confidentiality.

Study design and measurements.

This was a retrospective review of medical records for people with MDR/RR-TB who had received a bedaquiline-based regimen between January 2020 and December 2021 at three referral hospitals. We considered socio-demographic variables namely, age in completed years but later categorized as 15–24, 25–34, 35–44, and ≥ 45 years, sex (male or female), marital status, human immunodeficiency virus (HIV) serostatus, previous TB treatment, and current alcohol consumption as well as current smoking. Clinical variables included the bedaquiline-based regimen (categorized into all-oral bedaquiline-based regimen, individualized regimen, and long regimen), drug sensitivity test (DST) profile and year of TB treatment. Baseline data or data collected before treatment initiation for MDR/RR-TB such as weight in kilograms (kgs), height in meters, hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, potassium, and bilirubin were collected. Body mass index (BMI) was computed as weight in kilograms (Kg) divided by height in meters squared and categorized as underweight (BMI < 18.5 Kg/m2), normal (BMI 18.5–24.9 Kg/m2) and overweight/obese (BMI ≥ 25 Kg/m2). Hemoglobin was categorized as ≥ 11.6 g/dl in women versus ≥ 13 g/dl in men to depict the absence of anemia, and < 11.6 g/dl in women versus < 13 g/dl in men to depict the presence of anemia. Creatinine was considered normal if ≤ 114.9 umol/L and high if > 114.9 umol/L.

We regarded AST as normal if it was 8–33 U/L and high if > 33 U/L. ALT was considered normal if it was 4–36 U/L or high if > 36 U/L. Sodium was considered normal if it was 135–145 mmol/L, low if < 135 mmol/L, and high if > 145 mmol/L. Potassium was considered normal if it was 3.5–5.5 mmol/L, low if < 3.5 mmol/L, and high if > 5.5 mmol/L. Bilirubin was taken as normal if it was 1.71–20.5 umol/L and high if > 20.5 umol/L.

Definitions of treatment outcomes among people with MDR/RR-TB.

The TB treatment outcome data included:

i. Treatment completed was defined as an individual who completed treatment as recommended by the national policy but whose treatment outcome does not meet the definition for cure or treatment failure [13].
ii. Cured was defined as a person with bacteriologically confirmed pulmonary TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure [13].
iii. Died is defined as an individual who died before starting treatment or during the course of treatment [13].
iv. Lost to follow-up was defined as an individual who did not start treatment or whose treatment was interrupted for 2 consecutive months or more [13].
v. Treatment failed was defined as an individual whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy [13].
vi. Transfer out was defined as individuals who are transferred to another treatment unit [13].
vii. Treatment outcome not reported was defined as an individual for whom no treatment outcome was assigned [13].

We excluded participants without treatment outcome evaluation (transfer-out and treatment outcome not reported) as the treatment outcome could not be established. We defined treatment success as TB cure or treatment completed, expressed as a percentage, and reported as a binary outcome (yes vs. no).

Statistical analysis: statistical power and data analysis.

We hypothesized that treatment success will be lower among people with MDR/RR-TB with high AST levels compared to normal AST levels. We used this hypothesis to compute the statistical power as existing data were retrieved and analyzed since sample size computation was not needed. Regarding the data analysis, we descriptively summarized the numerical data using the mean and standard deviation as the data were normally distributed. We used frequencies and percentages for categorical data. We performed bivariable analysis to assess differences in the outcome with categorical variables using the Chi-squared test for larger cell frequencies (≥5) or Fisher's exact test for smaller cell frequencies (<5). For mean differences in the outcome with numerical data, we used the Student's *t*-test when the data were normally distributed otherwise the Mann-Whitney *U* test was employed. Factors independently associated with the outcome were determined using a multivariable modified Poisson regression analysis as the outcome was common, allowing for robust standard errors. We reported association using the risk ratio (RR) and corresponding 95 % confidence interval (CI). The analysis was conducted in Stata version 15.

3. Results

Characteristics of participants by treatment success among people with MDR/RR-TB on Bedaquiline-based regimen.

Of 82 records retrieved, 10 records without treatment outcome evaluation and 1 record for an individual with pre-XDR were excluded. We, therefore, analyzed data from 71 participants aged ≥ 15 years of whom 52 (73.2 %) were male, 29 (40.8 %) were married, and 46 (64.8 %) were newly diagnosed with MDR/RR-TB (Table 1).

Treatment outcomes among people with MDR/RR-TB on a bedaquiline-based regimen.

Of the 71 participants in Table 2, 13 (18.3 %) completed treatment, 46 (64.8 %) were cured, 8 (11.3 %) died, 4 (5.6 %) were lost to follow-up, and none (0.0 %) failed treatment. Of the participants, only 12 (16.9 %) were unsuccessfully treated while 59 (83.1 %) were successfully treated for MDR/RR-TB.

Factors associated with TB treatment success among people with MDR/RR-TBTB on bedaquiline-based regimen.

The factors associated with the treatment success are summarised in Table 3. In the unadjusted analysis, treatment success was more likely in males, those aged 25–34 years, and those who had MDR/RR-TB. Conversely, treatment success was less likely among participants with HIV, current alcohol consumers, current smokers, and those with higher AST. After adjusting for clinically relevant and statistically significant variables, current alcohol consumption and high AST were found associated with a lower likelihood of treatment success among people with MDR/RR-TB on bedaquiline-based regimen.

Statistical power analysis.

The TB treatment success was 92.7 % (38/41) among people with MDR/RR-TB with normal AST levels compared to 52.5 % (21/30) among those with higher AST. Using a 2-sided Chi-square test at a 5 % statistical significance level, the study had a 95.7 % statistical power in detecting an association between AST and TB treatment success among people with MDR/RR-TB.

4. Discussion

We studied the TB treatment outcomes and treatment success among people with MDR/RR-TB on a bedaquiline-based regimen at three referral hospitals in Uganda. We found a TB treatment success rate of 83.1 % and a mortality rate of 11.3 %. In our study, successful TB treatment is less likely among people with MD/RR-TB with higher AST levels and currently consuming alcohol.

The finding that the majority of people with MDR/RR-TB treated with a bedaquiline-based regimen achieved successful treatment is consistent with some earlier studies in South Africa [14–16]. Those studies were carried out in an environment with a high incidence of TB/HIV, where the racial and age distributions, HIV/TB coinfection, and anti-TB sensitivity test profile are comparable to our study. However, some of the previous studies in South Africa included people with pre-XDR-TB and XDR-TB but these categories of people with TB are excluded in the present study. Our finding of higher treatment success and lower mortality rates is not surprising as evidence from a *meta*-analysis of eight studies reported that treatment with a bedaquiline-based regimen lowers the risk of all-cause mortality among people with DR-TB [17].

Participants reporting current alcohol use or consumption at the time of the data collection had a lower likelihood of treatment success compared to those reporting no use or consumption of alcohol. A systemic review and *meta*-analysis of people with MDR/RR-TB, report that alcohol consumption was significantly associated with unsuccessful treatment outcomes [18]. Alcohol consumption in people with MDR/RR-TB may lead to drug malabsorption due to disrupted host defense mechanisms in the respiratory and gastrointestinal tracts [19–21]. Additionally, bedaquiline's hepatotoxic effects including elevation of bilirubin and transaminase levels are well-documented [22]. Therefore,

Table 1
Distribution of participant characteristics by treatment success among people with MDR/RR-TB on bedaquiline-based regimen.

Variables	Level	All (n = 71)	Treatment success		P-value
			No (n = 12)	Yes (n = 59)	
Age category (years)	15–24	7 (9.9)	2 (16.7)	5 (8.5)	0.482
	25–34	25 (35.2)	2 (16.7)	23 (39.0)	
	35–44	14 (19.7)	3 (25.0)	11 (18.6)	
	≥45	25 (35.2)	5 (41.7)	20 (33.9)	
	mean (SD)	38.7 (12.2)	41.5 (16.7)	38.2 (11.2)	0.392
Sex	Female	19 (26.8)	5 (41.7)	14 (23.7)	0.357
	Male	52 (73.2)	7 (58.3)	45 (76.3)	
Marital status	Married	29 (40.8)	7 (58.3)	22 (37.3)	0.194
	Separated	15 (21.1)	0 (0.0)	15 (25.4)	
	Single	21 (29.6)	5 (41.7)	16 (27.1)	
	Widow	2 (2.8)	0 (0.0)	2 (3.4)	
	Widower	4 (5.6)	0 (0.0)	4 (6.8)	
Previous TB treatment	No	46 (64.8)	9 (75.0)	37 (62.7)	0.631
	Yes	25 (35.2)	3 (25.0)	22 (37.3)	
TB treatment year	2020	39 (54.9)	4 (33.3)	35 (59.3)	0.183
	2021	46 (64.8)	8 (66.7)	24 (40.7)	
Xpert severity	High	22 (31.0)	3 (25.0)	19 (32.2)	0.719
	Low	20 (28.2)	5 (41.7)	15 (25.4)	
	Medium	16 (22.5)	2 (16.7)	14 (23.7)	
	Very low	13 (18.3)	2 (16.7)	11 (18.6)	
Bedaquiline-based regimen	All-oral regimen	59 (83.1)	8 (66.7)	51 (86.4)	0.162
	Individualized Regimen	11 (15.5)	4 (33.3)	7 (11.9)	
	Long Regimen	1 (1.4)	0 (0.0)	1 (1.7)	
DST profile	MDR-TB	49 (69.0)	10 (83.3)	39 (66.1)	0.404
	RR-TB	22 (31.0)	2 (16.7)	20 (33.9)	
HIV serostatus	Negative	37 (52.1)	5 (41.7)	32 (54.2)	0.633
	Positive	34 (47.9)	7 (58.3)	27 (45.8)	
Currently drinks alcohol	No	44 (62.0)	4 (33.3)	40 (67.8)	0.055
	Yes	27 (38.0)	8 (66.7)	19 (32.2)	
Currently smokes cigarette	No	55 (77.5)	7 (58.3)	48 (81.4)	0.173
	Yes	16 (22.5)	5 (41.7)	11 (18.6)	
Obesity	Normal	42 (59.2)	8 (66.7)	34 (57.6)	0.788
	Underweight	28 (39.4)	4 (33.3)	24 (40.7)	
	Overweight/ Obese	1 (1.4)	0 (0.0)	1 (1.7)	
Anemia	No	35 (49.3)	7 (58.3)	28 (47.5)	0.711
	Yes	36 (50.7)	5 (41.7)	31 (52.5)	

(*continued on next page*)

Table 1 (*continued*)

Variables	Level	All (n = 71)	Treatment success No (n = 12)	Yes (n = 59)	P-value
	mean (SD)	12.1 (2.1)	12.2 (2.5)	12.0 (2.0)	0.800
Serum sodium	Normal	44 (62.0)	8 (66.7)	36 (61.0)	0.512
	Low	21 (29.6)	4 (33.3)	17 (28.8)	
	High	6 (8.5)	0 (0.0)	6 (10.2)	
	mean (SD)	137.05 (8.20)	136.4 (5.3)	137.2 (8.7)	0.714
Serum potassium	Normal	69 (97.2)	11 (91.7)	58 (98.3)	0.757
	High	2 (2.8)	1 (8.3)	1 (1.7)	
	mean (SD)	4.5 (1.1)	4.96 (2.6)	4.4 (0.5)	0.146
AST	Normal	41 (57.7)	3 (25.0)	38 (64.4)	0.028
	High	30 (42.3)	9 (75.0)	21 (35.6)	
	mean (SD)	39.94 (27.3)	54.7 (36.4)	36.9 (24.3)	0.038
ALT	Normal	47 (66.2)	6 (50.0)	41 (69.5)	0.334
	High	24 (33.8)	6 (50.0)	18 (30.5)	
	mean (SD)	31.13 (24.9)	34.6 (19.2)	30.4 (25.9)	0.595
Bilirubin	Normal	69 (97.2)	12 (100.0)	57 (96.6)	1.000
	High	2 (2.8)	0 (0.0)	2 (3.4)	
	mean (SD)	4.7 (10.7)	3.4 (4.0)	5.0 (11.6)	0.644

Note: DST: Drug susceptibility testing; ALT: Alanine aminotransferase (ALT); AST: Aspartate aminotransferase; SD: Standard deviation.

Table 2
TB treatment outcomes among people with MDR/RR-TB on a bedaquiline-based regimen.

Variables	Level	No. (%)
Treatment outcome	Completed	13 (22.0)
	Cured	46 (78.0)
	Died	8 (11.3)
	Lost to follow-up	4 (33.3)
	Treatment failure	0 (0.0)
Treatment success	Yes	59 (83.1)
	No	12 (16.9)

it is recommended that those taking bedaquiline refrain from drinking alcohol and undergo routine hepatotoxicity monitoring [23]. However, because our study was retrospective in nature and alcohol consumption was assessed by self-reporting, we were unable to determine the precise quantity and kinds of alcohol consumed by each individual. As a result, the results may have overestimated or underestimated the relationship between alcohol consumption and treatment outcomes. Therefore, there is a need to provide psychosocial support and health education to people with MDR/RR-TB on the harmful effects of alcohol including the potential for alcohol and drug interactions, and treatment success.

Our finding that higher AST levels are associated with a lower likelihood of treatment success among people with MDR/RR-TB is unique as previous studies have not reported such results. Individuals with high AST might have a compromised liver function leading to impaired metabolism of anti-TB regimens, resulting in suboptimal drug levels and reduced treatment success. However, our data should be cautiously interpreted as additional studies replicating the findings are needed.

The strengths of our study include the analysis of data from three large referral hospitals in Uganda that treat a larger proportion of people with MDR/RR-TB. Our findings, therefore, provide a good picture of

Table 3
Factors associated with TB treatment success among people with MDR/RR-TB drug-resistant TB on bedaquiline-based regimen.

		Univariable analysis	Multivariable analysis
Variables	**Level**	**RR (95 % CI)**	**aRR (95 % CI)**
Sex	Female	1	1
	Male	1.17 (0.88–1.57)	1.24 (0.95–1.61)
Age group (years)	15–24	1	
	25–34	1.29 (0.79–2.09)	
	35–44	1.10 (0.64–1.90)	
	≥45	1.12 (0.67–1.87)	
HIV serostatus	Negative	1	
	Positive	0.92 (0.74–1.14)	
DST profile	MDR-TB	1	
	RR-TB	1.14 (0.94–1.39)	
Currently drinks alcohol	No	1	1
	Yes	0.77 (0.59–1.01)	0.78* (0.60–0.99)
Smokes cigarette	No	1	
	Yes	0.79 (0.56–1.12)	
AST	Normal	1	1
	High	0.76* (0.59–0.97)	0.77* (0.60–0.98)

Note: Risk ratios are the exponentiated coefficients at a 5 % level of statistical significance; 95 % confidence intervals in brackets; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

treatment success among people with MDR/RR-TB on bedaquiline-based regimens in the country. Our study is the first to describe the treatment outcomes and analyze the treatment success among people with MDR/RR-TB on a bedaquiline-based regimen in Uganda. However, there are some weaknesses report such as the smaller sample size although the statistical power was found to be sufficient. We analyzed data spanning a relatively shorter period (approximately 2 years) so a better trend in treatment success would be demonstrated if the data were analyzed for a longer period.

Current alcohol consumption was measured by self-reporting so the findings might have over or underestimated its association with treatment success. Current alcohol consumption should have better been measured and quantified using a validated tool such as the Alcohol Use Disorder Identification Test Consumption (AUDIT-C) tool. Also, data on the number of cigarettes smoked and smoking patterns are lacking as these data are not collected during routine TB care. These variables need to be included in the TB unit registers in order to promote operational research and improve the quality of TB care. As reported elsewhere [24], the possibility of data inaccuracies in the TB registers cannot be excluded as secondary data were retrieved and analyzed. However, we mitigated this problem through data validation before the data abstraction. There are also several unmeasured confounders as secondary retrospective data collected for routine TB care have been analyzed. These limitations should be considered as one interprets our findings.

Conclusions and recommendations.

We found treatment success among people with MDR/RR-TB on a **bedaquiline**-based regimen was relatively high, reinforcing its effectiveness in a real-world setting. We found high AST levels and current alcohol consumption are associated with a lower likelihood of treatment success. Therefore, among people with MDR/RR-TB on a bedaquiline-based regimen, there is a need to strengthen psychosocial support regarding the harmful effects of alcohol consumption and its interaction with drugs, including routine monitoring of liver function in order to enhance TB treatment success. More research is needed, in our opinion, to support the notion that treatment success among people with MDR/RR-TB on bedaquiline-containing regimens is negatively impacted by elevated aspartate aminotransferase levels.

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Ethics approval and consent.

We received approval from the Research and Ethics Committee of MUST (MUST-2022–443). A waiver of consent was also granted by MUST-REC and all the study methods were carried out following the relevant guidelines and regulations.

Authors contribution

Lodiong Jackson Dumo: Collected the data, wrote the discussion and reviewed the manuscript.

Jonathan Izudi: Formulated the research topic, analyzed the data, interpreted the results and reviewed the manuscript.

Boniface Lumori: Formulated the research topic, wrote the introduction and reviewed the manuscript.

CRediT authorship contribution statement

Lodiong Jackson Dumo Lodiong: . **Jonathan Izudi:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Boniface Amanee Elias Lumori:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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