

## Treatment Outcomes of Multi-Drug-Resistant Tuberculosis and Its Determinants in Boru Meda Hospital, Northeast Ethiopia

Assefa Mulu Baye<sup>1\*</sup>, Wondmagegn Demisis Sarhie<sup>2</sup> and Brhanu Teka Endalew<sup>3</sup>

<sup>1</sup>Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Ethiopia

<sup>2</sup>Department of Medical Laboratory Sciences, College of Medicine and Health Sciences, Wollo University, Ethiopia

<sup>3</sup>Department of Microbiology, Immunology and Parasitology, School of Medicine, College of Health Sciences, Addis Ababa University, Ethiopia

\*Corresponding author: Assefa Mulu Baye, Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Ethiopia, Tel: +251-9-10980410; E-mail: mulubaye@gmail.com

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### Abstract

**Background:** Multidrug-resistant tuberculosis remains a peril to the global tuberculosis control struggle. Ethiopia is one of the high burden countries and tuberculosis remains one of the leading causes of mortality. The prolonged treatment associated with multi-drug resistance tuberculosis and the often-severe adverse effects of second-line anti-tuberculosis agents increases the challenges to achieve treatment completion.

**Objectives:** The aim of this study is to assess the treatment outcomes of multidrug-resistant tuberculosis management and its determinants in Boru Meda Hospital.

**Methods:** A retrospective cohort study was employed for this study. All patients enrolled for multidrug-resistant tuberculosis management between December 2012 and 2016 were included in the study. Interim and final outcomes of multidrug-resistant tuberculosis treatment were collected from the multidrug-resistant tuberculosis registry. The demographic and clinical characteristics of cases, drug resistance and the treatment regimen, management and outcome were described. Chi-square test was used to calculate association factors with a successful treatment outcome.

**Result:** Totally, 141 patients were included for the study from December 18, 2012–June 7, 2016. Women were slightly greater than men patients, 53.2%. The mean age of the study participants was 30.87 years. Majority of the patients, 84.4%, had favorable interim treatment outcome at the end of six months. Totally, 61.1% patients were cured, 24.4% of them died, 8.9% were defaulted, 3.3% have completed, and 2.2% failed. Patients in the age group of ≤ 18 years and 19-29 years, and patients having a negative culture result by six months were associated with successful treatment outcome.

**Conclusion and recommendation:** The cure rate was about 60% and significant number of patients were died (24.4%). Strategies to reduce defaulters are crucial in the treatment of multidrug-resistant tuberculosis. The current results indicate that special attention should be paid to older patients.

**Keywords:** MDR-TB; Treatment outcome; Boru meda hospital

**Abbreviations** ADRs: Adverse Drug Reactions; AFB: Acid-fast *Bacilli*; DOT: Directly Observed Therapy; FMOH: Federal Ministry of Health; HIV: Human Immunodeficiency Virus; MDR-TB: Multidrug Resistance Tuberculosis; SPSS: Statistical Package for Social Science; TB: Tuberculosis; WHO: World Health Organization; XDR-TB: extensively Drug Resistance Tuberculosis

### Introduction

Multidrug-resistant tuberculosis (MDR-TB) is resistance of *M. tuberculosis* to at least isoniazid and rifampicin, which are the two most effective anti-tuberculosis drugs. Multidrug-resistant TB (MDR-TB) remains a threat to the global tuberculosis (TB) control effort [1].

Ethiopia is one of the high burden countries and TB remains one of the most important causes of mortality. Moreover, Ethiopia is one of

the high TB/HIV and multidrug resistant TB (MDR-TB) burden countries. According to the recent national TB drug resistance surveillance report, 2.3% of new TB cases and 17.8% of previously treated TB cases were estimated to have MDR [2].

The prolonged MDR-TB treatment and severe adverse effects of second-line antibiotics increases the challenges to achieve treatment success [3]. MDR-TB treatment requires complex, expensive treatment with less effective second line drugs, and is often associated with significant side effects. The minimum treatment duration is 20 months. Treatment outcomes for patients with MDR-TB are worse than for drug sensitive TB, with low success rates and high rates of treatment failure and default [4].

Improved study of treatment outcome monitoring of MDR-TB cases allows treatment regimens and management to be assessed and progress towards achieving targets set by WHO [5], to be evaluated over time. In the UK in 2010, the percentage of MDR-TB cases

completing treatment was 72.1% [6] which was below the WHO and UK treatment completion targets of 75% [5] and 85%, respectively [7].

Studies indicated that patients getting a fluoroquinolone or a bacteriostatic drug were more probable to have a successful treatment outcome compared to those who did not [6,8].

A study in Estonia, a European country with one of the highest MDR-TB and XDR-TB rates in the world, indicated that HIV infection and previous TB treatment increased the risk of poor treatment outcome. Alcohol abuse was close to be significantly associated with poor treatment outcome in MDR-TB [9].

Generally, several studies indicated that the outcome of MDR-TB management is unfavorably under optimal. In addition, there are different factors stated in the different settings of different countries. Information on the outcome of MDR-TB management and determinant factors is very limited in Ethiopia. Therefore, the aims of this study are to determine the percentage of MDR-TB patients completing treatment successfully attending Boru Meda Hospital MDR Center between 2012 and 2016, to describe the clinical characteristics of these patients and to examine factors associated with a successful treatment outcome, loss to follow up and death.

## Methods

A retrospective cohort study applied for this study in Borumeda Hospital MDR Center. The Hospital is located in Amhara Regional, Northeastern Ethiopia. It has launched MDR-TB management since December 2012, and totally there were 141 patients who had been enrolled for MDR-TB management.

The source populations of this study were all MDR-TB patients attending the hospital. All the patients who were attending in the MDR clinic of the hospital were included. Incomplete registries of patients on MDR-TB management outcome were excluded. Demographic and clinical characteristics of patients were obtained from the register of each patient enrolled for MDR-TB management in the hospital. Other current and baseline factors like HIV, receiving ART, the initial drug regimen for MDR-TB, treatment start date, details of changes in treatment, duration of treatment were gathered from their registry and medical records. Interim and final outcomes of MDR-TB treatment were also collected from the MDR-TB registry. Two BSc nurses were employed to collect data at the hospital.

To ensure the completeness, accuracy and consistency of data collection, a session was held every week of the data collection period. The data was checked to ensure that all the information has been properly collected and recorded. Data collectors were trained on the tools of the data collection and the objectives of the study.

Treatment for MDR-TB typically takes 20 months or more and final outcomes can therefore only be assessed two to three years after enrolment. However, an indication of how patients are responding may be needed much earlier, particularly when a drug-resistant TB treatment program has recently started. Culture conversion to negative (for confirmed pulmonary cases) in month six and death by six months are commonly used indicators of treatment response. Information on loss to follow-up by six months is helpful.

Interim MDR-TB treatment outcomes were assessed by determining MDR-TB cases with negative culture by six months, MDR-TB cases who died by six months and MDR-TB cases who were lost to follow-up by six months

The final outcome of treatment was also determined. All confirmed MDR-TB patients entered on the treatment register were assigned one of six mutually exclusive outcomes at the end of their therapy. These final treatment outcome indicators were cured, treatment completed, treatment failed, died, lost to follow-up and outcome not evaluated. Indicators were measured 24 months after the end of the year of assessment.

Statistical analyses were carried out using SPSS version 20. The demographic and clinical characteristics of cases, drug resistance and the treatment regimen, management and outcome were described. Outcome categories were based on criteria by Ditah et al. [10] Chi-square test was used to identify the association between the outcome variable and independent variables. P values less than 0.05 was considered to be statistically significant.

Ethical clearance was sought from Wollo University Ethical Review Committee. All information on patients remained confidential and shared only by the study team. In all cases, the principal investigator ensured that data collection forms and the completed identification code list were kept in locked files.

## Results and Discussion

### Patient characteristics

In total, 141 patients were included for the study in the MDR-TB center of Boru Meda Hospital from December 18, 2012–June 7, 2016. The main characteristics of these patients with MDR-TB included in the study are given in Table 1. Women patients were slightly greater than men patients, 75 (53.2%). The mean age of the study participants was 30.87 years (range, 3 to 75 years).

Variables		Frequency	Percent
Sex	Male	66	46.8
	Female	75	53.2
Age	≤ 18	9	6.4
	19-29	69	48.9
	30-40	42	29.8
	41-64	17	12.1
	>65	4	2.8

**Table 1:** Baseline characteristics of MDR-TB patients in Boru Meda Hospital, December 18 2012 to June 7, 2016.

### Baseline TB-related data

Tuberculosis was pulmonary in 96.5% of the cases and extra pulmonary in 9 cases (3.5%). Out of the MDR-TB cases, 42.6% were registered after failure of retreatment, as defined by the WHO, whereas, 30.5% were registered after failure of new regimen. The diagnosis of majority of the cases, 60.5%, was by gene Xpert. Culture was employed only in 5 cases to diagnose these MDR-TB cases (Table 2).

Variables		Frequency
Site of Disease	Pulmonary TB	136 (96.5%)

	Extra pulmonary TB	5 (3.5%)
<b>Registration Group</b>	New	12 (8.5%)
	Relapse	19 (13.5%)
	After Default	3 (2.1%)
	Failure of New Regimen	43 (30.5%)
	After failure of retreatment	60 (42.6%)
	Transfer in from other sites	2 (1.4%)
	Other	2 (1.4%)
<b>Diagnosis Method</b>	Line Prone Assay (LPA)	50 (35.5%)
	Gene Xpert	85 (60.5%)
	Culture	6 (4.2%)

**Table 2:** Clinical characteristics of MDR-TB patients in Boru Meda Hospital, December 18 2012 to June 7, 2016.

Three types of regimens were administered in the intensive phase management of MDR-TB cases. Majority, 83%, were on ethionamide-based regimen whereas only 17% were on prothionamide-based regimen. Of the injectables only 9.2% of the cases received kanamycin and the rest received capreomycin based regimen (Table 3).

Phase	Regimen*	Frequency (%)
Intensive phase (N=141)	Cm/Eto/Lfx/Cs/Z	104 (73.8%)
	Cm/Pto/Lfx/Cs/Z	24 (17%)
	E/Km/Eto/Lfx/Cs/Z	13 (9.2%)
Continuation Phase (N=90)	Eto/Cs/Lfx/Z	90 (98.9%)
	Pto/Cs/Lfx/Z	1 (1.1%)

\*Abbreviations—Cm: Capreomycin; Eto: Ethionamide; Lfx: Levofloxacin; Z: Pyrazinamide; Cs: Cyclosporine; Pto: Prothionamide; Km: Kanamycin.

**Table 3:** Treatment regimens of MDR-TB patients in Boru Meda Hospital, December 18 2012 to June 7, 2016.

### HIV Co infection

Among the 141 patients with MDR TB, 38 (27%) were found to be HIV-co-infected. From the HIV-TB co-infected cases majority 32 (84.2%) have received antiretroviral therapy (ART).

### Outcome of treatment

The interim treatment outcome of 141 patients was determined. Majority had favorable interim treatment outcome at the end of six month. Majority of patients, 84.4%, were having negative culture by six month. However, 15 patients were died by six month and 6 patients were found to be lost to follow up.

Variables	Overall treatment outcome	C2	P-value
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From the 141 MDR-TB patients, final treatment outcome of 90 patients was determined. In total, 61.1% patients were cured, 24.4% were died, 8.9% were defaulted, 3.3% had completed, and 2.2% were failed. Final treatment outcome was not evaluated for 51 of the cases (Table 4).

From the above table, it can be understood that final treatment success is achieved in 58 MDR-TB patients (64.4%). This is similar with a study done in Uzbekistan where treatment was successful for 54 (62%) patients (Cox HS, et al. [11]). In total, 22 (24.4%) patients who died over the three and half year's follow-up experienced a TB-related death (Table 4). Majority 15 (68.2%) were died by their six months of therapy.

Treatment outcomes	Number	Percent
Interim treatment outcomes (N=141)		
Negative culture by 6 month	119	84.4
Died by 6 month	15	10.6
Lost to follow up by 6 month	6	4.3
Total	141	100
Final treatment outcomes (N=90)		
Cured	55	61.1
Died	22	24.4
Lost to follow up	8	8.9
Treatment completed	3	3.3
Treatment failed	2	2.2
Total	90	100
Not Evaluated	51	36.2

**Table 4:** Treatment outcomes of MDR-TB management among patients in Boru Meda Hospital, December 18 2012 to June 7, 2016.

### Factors associated with treatment outcome

Chi-square test analysis was made to notice presence of statistically significant association between explanatory variables and the outcome variable. Final treatment outcome was categorized into successful treatment outcome (treatment completed and cured) and adverse treatment outcome (treatment failed, lost to follow up or died).

Age, default within six months and negative culture by six month were found to be statistically associated with MDR-TB treatment outcomes. Patients in the age group of ≤ 18 years and 19-29 years are associated with successful treatment outcome (P-value=0.005). On the other side patients having a negative culture result were associated with favorable treatment outcome (P-value=0). Likewise defaulted patients within six months were found to be associated with unsuccessful treatment outcome (P-value=0.011) (Table 5).

		Successful	Not successful		
Sex	Male	27 (67.5%)	13 (32.5%)	0.293	0.588
	Female	31 (62.9%)	19 (38.0%)		
Age (years)	≤ 18	4 (100.0%)	0 (0.0%)	14.79	0.005
	19-29	36 (75.0%)	12 (25.0%)		
	30-40	14 (58.3%)	10 (41.7%)		
	41-64	4 (40.0%)	6 (60.0%)		
	≥ 65	0 (0%)	4 (100.0%)		
HIV Test Result	Reactive	12 (52.2%)	11 (47.8%)	2.03	0.207
	Non-reactive	46 (68.7%)	21 (31.3%)		
Intensive phase regimen	E/Km/Eto/Lfx/Cs/Z	10 (76.9%)	3 (23.1%)	2.751	0.253
	Cm/Eto/Lfx/Cs/Z	48 (63.2%)	28 (36.8%)		
	Cm/Pto/Lfx/Cs/Z	0 (0.0%)	1 (100%)		
Lost to follow up by six month	Yes	1 (16.7%)	5 (83.3%)	6.404	0.011
	No	57 (67.9%)	27 (32.1%)		
Negative culture by six month	Yes	57 (82.6%)	12 (17.4%)	42.581	0.000
	No	1 (4.8%)	20 (95.2%)		

**Table 5:** Factors associated with treatment outcome of MDR-TB management among patients in Boru Meda Hospital, December 18 2012 to June 7, 2016.

## Conclusion and Recommendations

### Conclusion

Majority (84.5%) of the patients had favorable interim treatment outcome at the end of six month. However, 15 patients died by six month and only 6 patients were found to be lost to follow up.

From the 90 patients whose final treatment outcome was determined, 61.1% of patients were cured, 24.4% of them died, 8.9% were defaulted, 3.3% have completed treatment and 2.2% failed. Patients in the age group of <30 years, and patients having a negative culture result by six month were associated with successful treatment outcome. On the other side, defaulted patients within six months were found to be associated with unsuccessful treatment outcome.

### Recommendations

Strategies to reduce defaulters are crucial in the treatment of multidrug-resistant tuberculosis. The current results indicate that special attention should be paid to older MDR-TB patients. Further comparative studies to identify all possible factors related to MDR-TB treatment outcome are recommended.

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