Infection and Drug Resistance

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Treatment Outcome of MDR/RR TB in a Resource-Constrained Setup: A Four-Year Retrospective Analysis

Abdurahman Abibeker Omer[1], Meiraf Daniel Meshesha[2], Abraham Teka Ajema[3], Samuel D Yoo[4]

[1]Department of Internal Medicine, Dilchora Hospital, Dire Dawa, Ethiopia; [2]Department of Internal Medicine, Dilla University, Dilla, Ethiopia; [3]Clinical and treatment wing, ICAP at Columbia University, Hawassa, Ethiopia; [4]Department of Internal Medicine, Jimma University, Jimma, Ethiopia

Correspondence: Meiraf Daniel Meshesha, Tel +251 096 089 0307, Email meirafdanielm@gmail.com

Introduction: The emergence of drug resistance in TB treatment is a major public health threat. However, there are limited studies which are directed towards identifying factors that explain the gap in achieving treatment targets.

Objective: : This study aimed to assess the treatment outcome and its associated factors among patients with MDR/RR-TB in Dilchora Hospital Treatment Initiation Center from January 2014 to December 2018.

Method: : A retrospective cross-sectional study was conducted on patients with MDR/RR TB who initiated treatment between January 2014 and December 2018. Data were extracted from patient medical charts using a structured questionnaire. SPSS version 26 was used for analysis. Reports are presented using percentages and frequency. Independently associated factors for unfavorable outcome were identified using binary logistic regression model. Adjusted and crude odds ratio with 95% CI was used. P-value less than 0.05 was used to declare statistical significance.

Result: : A total of 146 patients were included in this study. The overall prevalence of unfavorable outcomes in this study for those with known outcomes was 8.6%. People living with HIV had a 6.47 times (95% CI: 1.14–36.68) increased odds of death as compared to those who are HIV negative. For every 1kg/m^2 increment in BMI, there was a 35.3% (AOR = 0.647; CI: 0.44–0.95) reduction in the odds of death as compared to those who had a 1kg/m2 lower BMI. Each additional month without culture conversion also increased the odds of death 2.24 times (95%CI: 1.08–4.66).

Conclusion & Recommendation: : The findings of our study showed an appreciably low poor treatment outcome for this outpatient program. HIV screening and early initiation of HAART, early identification and treatment of those who are underweight and a critical follow-up to the time of sputum culture conversion could help in further improving the outcomes.

Keywords: MDR/RR-TB, treatment outcome, Dire-Dawa

Introduction

World Health Organization (WHO) has declared anti-microbial drug resistance as one of the major public health threats to date. The first-line drugs are becoming no longer effective for treatment making infection control difficult with increased risk of transmission, morbidity and mortality.[1] Resistance to anti-tuberculosis (anti-TB) drugs as any other anti-microbial resistance could result from primary infection or may develop in the course of a patient's treatment. WHO uses five categories to classify drug-resistant tuberculosis: Isoniazid (INH)-resistant tuberculosis, Rifampin Resistant-tuberculosis (RR-TB), Multi-drug resistant tuberculosis (MDR-TB), Pre-extensively drug-resistant tuberculosis (pre-XDR-TB), and extensively drug-resistant tuberculosis (XDR-TB). Multidrug-resistant tuberculosis (MDR-TB) is a type of TB that is resistant to at least the two most effective first-line drugs; Rifampicin and Isoniazid. Globally, due to the increasing trend of cases both estimated and reported, it is a primary focus area; multiple efforts are being introduced to strengthen its early detection and treatment with its favorable outcomes.[2,3]

Estimating the MDR TB disease burden depends on the extent of bacteriological confirmation of TB cases and testing drug resistance using rapid molecular tests, culture methods, or sequencing technologies. In 2020 worldwide, 71% (2.1/3.0 million)

Received: 16 June 2022
Accepted: 12 August 2022
Published: 22 August 2022

of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance and among these, there were 132,222 (6.2%) cases of MDR/RR-TB.[2] A WHO estimation for MDR TB out of all TB cases occurred in 2020 was 3.3% among new TB cases and 17.7% among previously treated TB cases.[4] After the diagnosis of MDR-TB majority,86%, of the cases had access to treatment. Compared with drug susceptible TB, the treatments are more sophisticated regimens for longer duration with a higher potential for adverse drug reactions. The cumulative number of MDR/RR TB reported cases enrolled to care during 2018 −2020 was 482,683, which is 32% towards the global targets set to enroll in treatment by UN high high-level meeting on TB during a similar period.[2] In Ethiopia during 2016, the estimated number of MDR/RR-TB cases among pulmonary positive is 2900 (1800–4000). The proportion of MDR/RR-TB cases among patients 2.7% while among previously treated cases is 14%. Since 2009, Ethiopia has started providing MDR/RR-TB treatment with parallel expansion of diagnostic setups in the country. So far, until 2016, there were 2820 cumulative cases enrolled in second-line TB treatment since 2008.[5]

The global treatment success rate in 2016–2018 for MDR/RR-TB ranged from 56% to 59%.[2] The Ethiopian MDR/RR-TB treatment cure rate in 2016 for cohorts put on treatment 24 months earlier was 49%, with treatment success rate of 70.9%, death rate of 10.5% and 10.5% of them were not evaluated during similar period.[5] Another multi-center study conducted in four MDR-TB centers in southern Ethiopia from 2014 to 2019, found a similar cure rate of 48.76% and a higher unfavorable treatment outcome than the global goal in ending the TB epidemic. Factors such as hospitalizations for care, male sex, and low hemoglobin level increased the risk of unfavorable treatment outcomes.[6] In a national TB service quality assessment across Ethiopia, the treatment success rate for DR-TB patients was 70%. Three percent of the patients failed DR-TB treatment and were moved to pre-XDR drug-resistant TB treatment; 10% died during treatment; and 11% were loss-to-follow-up (LTFU).[7]

There were lower rates of treatment success as compared to the national targets of 86% for the year 2019[5] in terms of treatment outcome with limited factors that determine the status for further intervention. Even though there are some studies conducted on MDR/RR TB in the country, we did not find any coming from the eastern part of Ethiopia. Additionally, the center was only receiving patients who were stable enough for outpatient care and our study allows to assess the treatment outcome in this setting. Therefore, this study aimed to assess the treatment outcome and associated factors among outpatient MDR/RR-TB patients in Dire Dawa administration of Dil-Chora Hospital from January 2014 to December 2018.

Methods and Materials

Study Area and Period

The study was conducted in Dire Dawa city administration, DilChora Hospital treatment initiation center through retrospective review of medical records of all patients with MDR/RR-TB enrolled between 2014 and 2018. Dire Dawa administration is one of the two city administrations, located in eastern part of Ethiopia at 501 km from Addis Ababa, capital city of Ethiopia. With regard to the MDR-TB service; two hospitals (one treatment initiating center and one treatment follow-up center), and five health centers for treatment follow-up are providing MDR-TB treatment services. Dire Dawa established one of the ten MDR-TB treatment initiating centers in 2013. Since then, more than 150 MDR/RR-TB patients (by the end of 2018) are enrolled into the treatment center.

The study was conducted from February 1, 2021 – May 31, 2021.

Study Design

A cross-sectional, retrospective study was carried out.

Source Population

All records of patients with MDR/RR-TB that were ≥15 years of age, enrolled into Dilchora Hospital treatment initiation center from January 2014 to December 2018 were included.

Study Population

All records of eligible patients with MDR/RR-TB who were enrolled in Dilchora Hospital treatment initiation center from January 2014 to December 2018 were included.

Diagnostic Techniques

GeneXpert MTB/RIF assay was used to identify patients with MDR/RR TB and enroll them into the treatment center. Afterwards, samples were taken for culture and drug sensitivity test (DST). DST for second-line anti-TB drug was done only for selected patients with high risk of resistance to second-line drugs like history of previous exposure to second-line anti-TB drugs for more than 1 month and history of household contact with a patient diagnosed with TB with a resistant strain to fluoroquinolones and/or second-line injectables. Sputum culture and smear were repeated on a monthly basis after initiation of treatment.

Chest X-rays were evaluated and documented by radiologists.

Treatment of MDR-TB

All of the treatment regimens were adopted from the national guidelines on drug resistant TB from ministry of health.[8]

Standardized regimens were initiated for all patients with MDR/RR TB. Regimen then was shifted to individualized protocol if DST showed resistance to fluoroquinolones or second-line injectables.

The standardized treatment regimen consisted of an intensive phase which lasts at least 8 months and at least four months after the patient becomes culture-negative taking whichever is the longest. Treatment continued for a minimum of 20 months and at least 18 months after the patient becomes culture-negative—whichever is longer. Regimen was a combination of ethambutol, pyrazinamide, kanamycin/amikacin, levofloxacin, ethionamide and cycloserine.

Individualized treatments were adjusted based on drug and sensitivity test result. MDR-TB patients susceptible to quinolone but resistant to kanamycin, regimen consisted of ethambutol, pyrazinamide, capreomycin, levofloxacin, ethionamide and cycloserine; MDR-TB patients susceptible to kanamycin but not ofloxacin regimen consisted of ethambutol, pyrazinamide, kanamycin/amikacin, moxifloxacin, ethionamide, cycloserine and para-aminosalicylic acid.

In both cases, patients came daily to the treatment center for direct observation treatments (DOTs) during the intensive phase. The second-line injectables were administered by nurses or health officers.

Afterwards, patients continued the DOT in their place of convenience with health-care worker or trained community member supervision till end of treatment, while the center communicated the DOT provider and the patient weekly through a phone call, thereby ascertaining compliance. Patients came to the hospital every month for a clinical evaluation. Sputum smear and culture were also evaluated monthly after initiation of treatment.

Patients with HIV coinfection who were already initiated on highly active anti-retroviral therapy (HAART) continued the HAART together with the MDR-TB treatment. HAART was initiated within 8 weeks of MDR-TB treatment initiation in those who were not already on HAART.

Data Collection Procedure

Data were extracted using a structured questionnaire from patient treatment charts, bacteriological laboratory reports, and radiological reports.

Dependent and Independent Variables

Dependent Variable

Treatment outcome; Favorable/Unfavorable.

Independent Variable

Sex, AGE (years), BMI (kg/m2), Hemoglobin (g/dl), Baseline creatinine, Anti-TB exposure, HIV status, Comorbidity other than HIV, Drug sensitivity test, Radiologic pattern, Treatment delay, Time till culture conversion, Presence of ADR

Age cut-off of 35 was used as beyond it was associated with unfavorable outcomes in other studies.[9]

A cut-off for creatinine of 1.2 mg/dl was used to differentiate normal vs abnormal levels.[10]

A cut-off of 60 days was used as a significant delay in MDR-TB treatment initiation from diagnosis.[11]

Data Quality Control

A check list was adapted from the medical registration book of MDR/RR-TB and was modified according to the study variable included and the specific context. The data collectors and supervisor were trained before data collection. The collected data was cross checked for consistency between patient treatment charts, bacteriological laboratory reports, and radiological reports. Double data entry and validation was conducted by principal investigator.

Data Analysis

All the collected data were coded entered and cleaned using Epi-Data version 3.1. Statistical analysis was conducted using SPSS version 26.

Descriptive statistics such as frequency and percentage were used for categorical variables.

Independently associated factors of treatment outcome were identified using binary logistic regression model. Adjusted and crude odds ratio with 95% CI was used. P-value less than 0.25 on bivariate analysis was used to identify variables for multivariate analysis. A P-value less than 0.05 on multivariate analysis declared statistical significance.

Operational Definition

Cured

Bacteriologically confirmed MDR/RR-TB patient who has completed treatment according to programmed protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatments. If only one positive culture is reported during the time and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured.[8]

Died

A patient who dies for any reason during the course of treatment.[8]

Drug Interruption

A patient whose anti-TB treatment was interrupted for less than two consecutive months after receiving for at least 1 month.[8]

Favorable Outcome

A case with either a “cured” or “treatment completed” outcome.

Individualized Treatment

Each regimen is adopted according to guidelines based on the patient’s past history of TB treatment, individual 1st line and 2nd line-DST results and possible side-effects.[8]

Loss-to-Follow-Up

A patient whose anti-TB treatment was interrupted for two or more consecutive months for any reason without medical approval.[8]

MDR-TB

TB caused by a drug resistant strain to at least isoniazid and rifampicin.

RR-TB

TB caused by a drug resistant strain to rifampicin without INH resistance.

Standardized Treatment

Data from representative patient populations used to base regimen design in the absence of individual DST.[8]

Transfer Out

MDR-TB patient who has been transferred to another reporting or recording unit and for whom the treatment outcome is unknown.[8]

Treatment Completed

In a bacteriologically confirmed MDR/RR-TB patient who has completed treatment according to the national treatment protocol but does not meet the definition of cured because of lack of bacteriological results.[8]

Treatment Delay

Defined as the duration between the date of MDR/RR-TB confirmation and date of treatment initiation.

Treatment Failure

In a bacteriologically confirmed MDR/RR-TB, if two or more of five cultures in the final 12 months of therapy are positive or if any one of the final three cultures is positive.

Treatment Interrupter

Patients who have discontinued anti-TB treatment for less than 02 months.[8]

Unfavorable Outcome

An outcome of "death" or "treatment failure".

Results

All of the one hundred forty six patients who were initiated on MDR-TB treatment in the center during the study period were included in the study.

Socio-Demographic Characteristics

The mean age in this study was 29.64 years, with the majority (87, 59.6%) of the patients being in the age category of 14–29. Males accounted for more than half (87, 59.6%) of the participants (Table 1).

Baseline Clinical Characteristics of Patients

The prevalence of HIV positivity in this study was 17.8% (26 of 146). About 26% (38) of patients had at least one comorbidity. The most common comorbidity seen was COPD (24,16.4%) followed by Diabetes Mellitus (9,6.1%). About

Table 1 Socio Demographic Characteristics of MDR/RR-TB Patient Who Were on Treatment in Dilchora Hospital, Dire Dawa City Administration, Eastern Ethiopia (n = 146)

Variables	Frequency	Percentage%
Age (years)		
14–29	87	59.6
30–44	34	23.3
45–59	23	15.8
≥60	2	1.4
Sex		
male	87	59.6
Female	59	40.4

Table 2 Baseline Clinical Characteristics of MDR/RR-TB Patients in Dilchora Hospital, Dire Dawa, Eastern Ethiopia (n = 146)

Variables	Frequency	Percentage%
HIV status of the patients		
Positive On HAART Not on HAART	26 24 2	17.8 92.3% 7.7%
Negative	120	82.2
Presence of comorbidity		
None	108	74
COPD	24	16.4
DM	9	6.1
HTN	2	1.4
Others	3	2.1
Anthropometric measurement (BMI)		
BMI	Mean =17Kg/m^2±3.2	
< 18.5 kg/m^2	109	74.7
18.5–25 kg/m^2	34	23.3
>25 kg/m^2	3	2.1
History of previous TB treatment		
New	26	17.8
Treated with first line	115	78.8
Treated with second line	5	3.4
History of treatment interruption		
Yes	49	33.6
No	96	65.8
Delay of treatment initiation		
<2 month	111	77.6
≥2 months	32	22.4

three-quarters (109) of the patients were underweight with a BMI <18.5kg/m^2; Only three patients had a BMI >25kg/m^2 (Table 2).

The majority of patients (120,82.2%) had a treatment history with either first-line or second-line anti-TB drugs. Only 26 (17.8%) patients were naïve to any type of anti-TB regimen. There was a history of treatment interruption in the prior course of treatment in 49 (33.6%) of the patients.

After diagnosis of MDR/RR-TB, there was a delay in initiation of treatment for more than 60 days in 32 (22.4%) patients (Table 2).

Table 3 Laboratory Characteristics of MDR/RR-TB Patients in Dilchora Hospital, Dire Dawa, Eastern Ethiopia (n = 146)

Variables	Frequency	Percentage%
Hemoglobin		
<12	91	62.3
≥12	55	37.7
Baseline serum creatinine		
<1.2	138	94.5
≥1.2	8	5.5
Smear grading at base line		
+ 3 smear	32	21.9
+2 smear	37	25.3
+1 smear	39	26.7
Scanty	21	14.4
Negative	17	11.7
Baseline DST result		
RIF resistance only	76	52.1
Resistance to RIF, INH	63	43.2
Resistance to RIF, INH, EMB, SM	7	4.8
Radiological (x-ray) pattern of lung lesion		
Cavitary lesion	58	39.7
Consolidative	28	19.2
Reticulonodular	24	16.4
None	36	24.7
Radiological extent of lung lesion		
Unilateral	51	34.9
Bilateral	59	40.4
None	36	24.7

Laboratory and Chest x Ray Characteristics

More than half (91,62.3%) of the patients in this study had a baseline hemoglobin level which is less than 12g/dl. On the other hand, a baseline serum creatinine was less than 1.2mg/dl in 138 (94.5%) participants (Table 3).

The baseline smear grading was at least +1 in 73.9% (108) of patients, while only 11.7%[17] of the patients were smear negative. DST showed resistance to rifampicin only in 76 (52.1%) patients while 63 (43.2%) patients were resistant to rifampicin and isoniazid (Table 3).

The most common radiologic finding in this study was a cavitary lesion. Fifty-eight patients (39.7%) had a cavitary lesion while reticule-nodular and consolidative pattern were seen in 24 (16.4%) and 28 (19.2%) patients, respectively. On the contrary, the chest x-ray was found to be normal in 36 (24.7%) patients.

Table 4 MDR/RR-TB and Treatment-Related Characteristics of MDR-TB Patients in Dilchora Hospital, Dire Dawa, Eastern Ethiopia (n = 146)

Site of MDR-TB		
Pulmonary	145	99.3
Extra pulmonary TB	1	0.7
Treatment regimens		
Standard regimens	142	97.3
Individualized regimens	4	2.7
Month of first culture conversion	Median= 2 month	
<2 month	46	31.7
2 month	55	37.9
>2 month	44	30.4
Adverse drug reaction of treatment		
Yes	130	89.0
No	16	11.0
Type of adverse drug reaction		
Hepatitis (jaundice)	3	2.3
GI upset	101	77.7
Renal toxicity	7	5.4
Psychiatric illness	8	6.2
Ototoxicity	3	2.3
Severe hypokalemia	6	4.6
Others	2	1.5

There was radiologic evidence of both lung involvement in 59 (40.4%) patients on chest x-ray while a unilateral lung involvement was seen in 51 (34.9%)(Table 3).

MDR-TB and Treatment-Related Characteristics

Almost all, 145, of the patients in this study had pulmonary tuberculosis except for one individual who had an extrapulmonary TB. Similarly, a standard regimen was given for the 142 (97.3%) patients while only 4 (2.7%) patients received an individualized regimen. The 4 patients who were started on individualized treatment were patients who were reinitiated on MDR retreatment after being lost-to-follow-up and DST showed resistance to ofloxacin in 3 of them and resistance to kanamycin was observed in one patient.

The median time for culture conversion from positive to negative was at 2 months. About one-third (44) of the patients had a culture conversion beyond 2 months (Table 4).

The majority (130,89%) of the patients, who were taking treatment for MDR-TB, had some form of adverse drug reaction. Gastrointestinal complaints were the most common of all, being present in 101 (77.7%) patients. Psychiatric illness (8,6.2%), renal toxicity (7,5.4%), and severe hypokalemia (6,4.6%) were also among the most frequently observed adverse drug reactions following GI upset (Table 4).

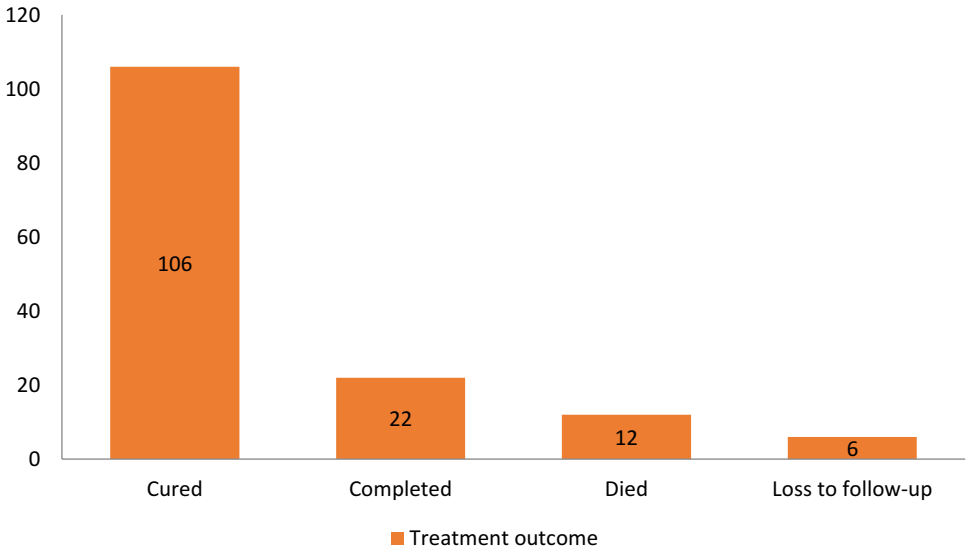

Figure 1 Magnitude of treatment outcome of MDR/RR-TB patients who were on treatment in Dilchora Hospital, Dire Dawa city administration, Eastern Ethiopia (n = 146), 2014–2018.

Drug adherence was more than 95% in 140 (95.9%) patients with the loss-to-follow-ups accounting for the entire poor drug adherence.

Treatment Outcomes

The overall prevalence of unfavorable outcomes (death and treatment failure) in this study for those with known outcomes was 8.6% (12 of 140). As can be seen from Figure 1, most of the patients (128, 91.4%) had a favorable outcome, either being cured or having completed treatment. Six patients (4.1%) were lost from follow-up and had an unknown outcome status

Bivariate and Multivariate Analysis

On bivariate analysis age, BMI, hemoglobin level, baseline creatinine, HIV status, comorbidity, and time till culture conversion were found to have a P-value <0.25 and hence became candidates for multivariable analysis (Table 5).

In multivariable analysis, three independent variables were significantly associated with unfavorable outcome (death in this case) for MDR treatment. Patients who were HIV positive had a 6.47 times increased odd of death as compared to those who were HIV negative. On the other hand, for every 1kg/m^2 increment in BMI, there was a 35.3% reduction in the odds of death as compared to those who had a 1kg/m^2 lower BMI.

The odds of death also increased 2.24 times for each additional month without culture conversion compared to those who converted a month earlier (Table 6).

Discussion

This study was designed to assess treatment outcomes and determine the factors associated with unfavorable treatment outcomes of MDR/RR-TB patients treated as outpatients in the ambulatory model of care in Dil-chora Hospital, Eastern Ethiopia. The prevalence of unfavorable outcomes among those with known outcomes was 8.6% which was dominated by patients' death. We also found that the overall treatment success (ie, having an outcome of cured or treatment completed) at the end of the treatment (24 months) was 87.7% (95% CI), which is in accordance with the WHO target (75–90%)[12] and the treatment outcomes so far done for inpatient model of care in Addis Ababa at St peter hospital in 2015 (78.6%).[13] This favorable outcome is higher than findings in other resource-constrained countries such as Egypt and India (78)[14,15] and also high-income countries such as Switzerland (76%),[16] the United Kingdom (70.60%);[17] and the United States of America (78%).[18]

Table 5 Bi-Variate Analysis of Variables for MDR/RR-TB Patients in Dilchora Hospital, Dire Dawa, Eastern Ethiopia (n = 140)

Variable	Category	Frequency	COR	P-value
Sex	Male	84	1	0.902
	Female	56	1.078	
AGE (years)	<35	96	1	**0.045**
	≥35	44	3.443	
BMI (kg/m^2) *	-	-	0.643	**0.009**
Hemoglobin (g/dl) *	-	-	0.877	**0.057**
Baseline creatinine	<1.2	132	1	**0.111**
	≥1.2	8	4.067	
Anti-TB exposure	No exposure	26	1	0.358
	Exposed	114	2.67	
HIV status	Negative	114	1	**0.001**
	Positive	26	8.032	
Comorbidity other than HIV	Yes	37	3.129	**0.063**
	No	103	1	
Drug sensitivity test	Rif only resistance	76	1	0.363
	Rifampicin+ at least 1 other	64	1.744	
Radiologic pattern	Cavitary	58	1	0.53
	Non cavitary	82	0.684	
Treatment delay	<60 days	108	1	0.288
	≥60 days	29	2.00	
Time till culture conversion*	-	-	1.711	**0.018**
Presence of ADR	Yes	125	1.351	0.781
	No	15	1	

Notes: *Continuous variable – category doesn't apply. Bold text – P-value <0.25.

This encouraging outcome may have several reasons, which could be related to the study population or the treatment program. The patients in our study were generally younger, with a mean age of 30 years (30 ±12SD), and were stable patients capable of having follow-up as an outpatient from the start. This may have contributed to the high-rate favorable outcome. In addition, after initiating treatment at an outpatient ambulatory model of care, all patients were followed closely at the treatment initiation center during the first month of treatment receiving directly observed therapy. In the continuation phases of treatment, patients were followed and traced using several strategies: health professionals from the treatment centers visited the patients every month; the patients were appointed monthly to visit the treatment initiation site; treatment supporters were assigned from the patient's family to assist the patient with directly observed therapy, and food baskets were provided regularly for the patient.

Yet, the treatment center was a new outpatient model of care, relatively treatment-inexperienced with advanced disease, with substantially high HIV-coinfection rate, and nearly three-thirds of the patients were underweighted (BMI

Table 6 Multi –Variable Model Showing Significantly Associated Variables

Variable	Category	Frequency	AOR	95% CI	P-value
Age	<35	85	1	-	0.158
	≥35	44	3.324	0.63–17.58	
Hemoglobin*	-	-	1.007	0.81–1.25	0.952
Creatinine	<1.2	122	1	-	0.164
	≥1.2	7	5.765	0.49–68.07	
HIV	Negative	103	1	-	**0.035**
	Positive	26	6.466	1.14–36.68	
Comorbidity	Yes	37	1.991	0.33–12.04	0.453
	No	92	1	-	
BMI*	-	-	0.647	0.44–0.95	**0.025**
Time till culture conversion*	-	-	2.241	1.08–4.66	**0.031**

Notes: *Continuous variable – category doesn't apply. Bold text – P-value <0.05.

<18.5). Thus, the outcomes could be described as outstanding and in contrast to reports of high mortality and lower treatment success rates (40–62%) for patients with MDR/RR TB treated elsewhere in Africa.[12,19–21]

Since the first reports of MDR TB in the early 1990s, HIV coinfection has been associated with poor outcomes in patients with MDR TB.[16–18] In more recent studies, unfavorable treatment outcomes have been higher among HIV co-infected patients.[22,23] The findings from our study also showed that unfavorable treatment outcome was statistically significantly associated with HIV coinfection. Strikingly, however, our treatment success rate (73%) among HIV co-infected patients was higher, and unfavorable outcome (27%) lower than reported elsewhere in sub-Saharan Africa.[14,19–21,24] This could have been due to the effective use of ART drugs since most of our patients here were on HAART at the time of diagnosis.

Sputum culture conversion is an important indicator of treatment response that also determines the duration of MDR/RR-TB treatment. Multiple previous studies have shown that sputum culture conversion is a strong predictor of unfavorable MDR-TB treatment outcome.[18,19] This was also witnessed from our study where the odds of death increased 2.24 times for each one additional month without culture conversion as compared to those who converted a month earlier. Around 70% of patients in our study had a sputum culture conversion at 2 two months or less, and the 30% achieved sputum culture conversion after 2 months.

Another important variable which was found to have a significant association with unfavorable treatment outcome was the body mass index. About 75% of the patients were underweight (BMI <18.5) in our study. More importantly, all deaths were seen in this subset of the study population. Controlling for other factors, our study found that for every 1kg/m^2 increment in BMI, there was a 35.3% reduction in the odds of death as compared to those who had a 1kg/m^2 lower BMI. BMI as a predictor for poor treatment was also seen in many other studies.[25,26]

Adverse drug effects in this study were encountered in most patients, with gastrointestinal toxicity, psychiatric illness, renal toxicity and hypokalemia as the most frequent adverse drug effects. But they were not found to be significantly associated with the treatment outcome in contrast to reports from studies on MDR-TB treatment outcomes elsewhere.[13,24] This may be due to the small sample size and incomplete documentation of the severity of the side effects from the retrospective records that we used. The recent update from WHO with regard to the use of 6-month bedaquiline, pretomanid, linezolid (600 mg) with or without moxifloxacin in place of the previous regimens for those with no prior exposure to any of the drugs might lead the way towards reducing prolonged exposure while maintaining safety and efficacy in the treatment of MDR/RR TB.[27]

Strengths and Limitations of This Study

Strength

This study is the first of its type to assess treatment outcomes in this specific outpatient MDR center where people with different socio demographic and cultural backgrounds are served. The study tried to assess factors for unfavorable outcomes by excluding patients who were lost to follow up, unlike many other studies, since their outcomes cannot really be ascertained. By doing so, factors can be assessed as to their real biologic effect.

Limitation

Since the data that was used was a secondary data, there were some issues with regard to data completeness. The cross-sectional nature of the study design also cannot ascertain the cause-and-effect relationship between variables. Additionally, the small number of cases in the study might have limited the statistical power of the study.

Conclusion and Recommendation

The findings of our study showed an appreciably low poor treatment outcome for this outpatient program targeting MDR/RR-TB in Dire Dawa, Dilchora hospital. This was achieved amid large resource constraints and with a substantial HIV burden. Poor treatment outcome of MDR/RR-TB was associated with HIV sero-positivity, having lower BMI and a delayed time to culture conversion.

HIV screening should be reemphasized among MDR/RR-TB patients for early initiation of ARTs. Early identification and treatment of those who are underweight and a critical follow-up to the time to sputum culture conversion could help in directing our efforts towards reducing further death and increasing rates of favorable outcomes.

Data Access

All authors of this manuscript had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics Approval

Ethical approval was received from Dire Dawa Regional Health Bureau and Dil-Chora hospital for using the information in the medical records of the patients. As the data used was a secondary data (from patients' chart) and there was no contact with actual patients, permission was only taken from the hospital manager for accessing and using this data, while keeping the confidentiality and privacy of the patients'. We confirm that our study complies with the Declaration of Helsinki.

Acknowledgments

The authors would like to thank members of Dilchora hospital administration for their cooperation during data collection.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosure

The authors report no conflicts of interest in this work.

References

1. World Health Oraganiztion. Antimicrobial resistance [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed August 15, 2022.
2. World Health Organization. Global tuberculosis report 2021 [Internet]. Geneva: World Health Organization; 2021. Available from: https://www.who.int/publications-detail-redirect/9789240037021. Accessed August 15, 2022.
3. Mirzayev F, Viney K, Linh NN, et al. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. *Eur Respir J*. 2021;57(6):2003300. doi:10.1183/13993003.03300-2020

4. World Health Organization. Global tuberculosis report 2020 [Internet]. Geneva: World Health Organization; 2020. Available from: https://www.who.int/publications-detail-redirect/9789240013131. Accessed August 15, 2022.
5. FMoH. National strategic plan tuberculosis and leprosy control 2006 – 2013 EC (2013/14 – 2020); 2017.
6. Bogale L, Tsegaye T, Abdulkadir M, Akalu TY. Unfavorable treatment outcome and its predictors among patients with multidrug-resistance tuberculosis in Southern Ethiopia in 2014 to 2019: a multi-center retrospective follow-up study. *Infect Drug Resist*. 2021;14:1343–1355. doi:10.2147/IDR.S300814
7. Khatri U. *Quality of Tuberculosis Services Assessment in Ethiopia*. Chapel Hill, NC, USA: University of North Carolina; 2020.
8. FMoH. Guidelines on programmatic management of drug resistant tuberculosis in Ethiopia; 2013.
9. Nandini S, Ashwani K, Shivani C, et al. Trends & treatment outcomes of multidrug-resistant tuberculosis in Delhi, India (2009–2014): a retrospective record-based study. *Indian J Med Res*. 2020;151(6):598–603. doi:10.4103/ijmr.IJMR_1048_18
10. Pagana KD, Pagana TJ, Pagana TN. *Mosby's Diagnostic & Laboratory Test Reference*. 14th ed. St. Louis, Mo: Elsevier; 2019.
11. Chen Y, Yuan Z, Shen X, Wu J, Wu Z, Xu B. Time to multidrug-resistant tuberculosis treatment initiation in association with treatment outcomes in Shanghai, China. *Antimicrob Agents Chemother*. 2018;62(4):e02259–17. doi:10.1128/AAC.02259-17
12. World Health Organization. *World Health Organization Multidrug and Extensively Drug-Resistant TB (M/XDR-TB): 2010 Global Report on Surveillance Andresponse*. Geneva, Switzerland. Geneva Switz: WorldHealthOrganization; 2010.
13. Meressa D, Hurtado RM, Andrews JR, et al. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax*. 2015;70(12):1181–1188. doi:10.1136/thoraxjnl-2015-207374
14. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. 2010;181(1):80–86. doi:10.1164/rccm.200907-0989OC
15. Patel SV, Nimavat KB, Alpesh PB, et al. Treatment outcome among cases of multidrug-resistant tuberculosis (MDR TB) in Western India: a prospective study. *J Infect Public Health*. 2016;9(4):478–484. doi:10.1016/j.jiph.2015.11.011
16. Helbling P, Altpeter E, Egger JM, Zellweger JP. Treatment outcomes of multidrug-resistant tuberculosis in Switzerland. Swiss Med Wkly; 2014 Available from: https://smw.ch/article/doi/smw.2014.14053. Accessed August 15, 2022.
17. Anderson LF, Tamne S, Watson JP, et al. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. *Eurosurveillance*. 2013;18(40):20601. doi:10.2807/1560-7917.ES2013.18.40.20601
18. Marks SM, Flood J, Seaworth B, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007. *Emerg Infect Dis*. 2014;20(5):812–821. doi:10.3201/eid2005.131037
19. FMoH. Training material on programmatic management of drug resistant tuberculosis in Ethiopia for GHWs facilitators' guide; 2012.
20. Giovanni Battista M, Dheda K, Centis R, et al. Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa. *Trop Med Int Health*. 2010;15(9):1052–1066. doi:10.1111/j.1365-3156.2010.02581.x
21. Marais E, Mlambo CK, Lewis JJ, et al. Treatment outcomes of multidrug-resistant tuberculosis patients in Gauteng, South Africa. *Infection*. 2014;42(2):405–413. doi:10.1007/s15010-013-0572-2
22. Gandhi NR, Andrews JR, Brust JCM, et al. Risk factors for mortality among MDR- and XDR-TB patients in a high HIV prevalence setting. *Int J Tuberc Lung Dis*. 2012;16(1):90–97. doi:10.5588/ijtld.11.0153
23. Kurbatova EV, Taylor A, Gammino VM, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis*. 2012;92(5):397–403. doi:10.1016/j.tube.2012.06.003
24. Satti H, McLaughlin MM, Hedt-Gauthier B, et al. Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. *PLoS One*. 2012;7(10):e46943. doi:10.1371/journal.pone.0046943
25. Kassa GM, Tadesse A, Gelaw YA, et al. Predictors of mortality among multidrug-resistant tuberculosis patients in central Ethiopia: a retrospective follow-up study. *Epidemiol Infect*. 2020;148. doi:10.1017/S0950268820002514
26. Ayinalem A, Bitew ZW, Worku T. Poor treatment outcome and its predictors among drug-resistant tuberculosis patients in Ethiopia: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;1(98):420–439.
27. World Health Organization. *Rapid Communication: Key Changes to the Treatment of Drug-Resistant Tuberculosis*. World Health Organization; 2022.