MULTI-DRUG RESISTANT TUBERCULOSIS TREATMENT OUTCOMES AND ASSOCIATED FACTORS IN BULE HORA GENERAL HOSPITAL, SOUTHERN ETHIOPIA: CROSS-SECTIONAL STUDY.

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ASSESMENT OF MDR TUBERCULOSIS TREATMENT OUTCOME AND ASSOCIATED FACTORS IN BULE HORA GENERAL HOSPITAL, SOUTHERN ETHIOPIA: A CROSS-SECTIONAL STUDY.

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Abstract

Background: Drug-resistant TB continues to be a public health threat. In Ethiopia even though MDR-TB treatment in ambulatory set up like Bule Hora General Hospital was started in 2014, the treatment outcome was not assessed in many centers.

Objective: To assess the Multidrug resistant tuberculosis (MDR-TB) patient treatment outcomes and associated factors at Bule Hora General Hospital, south Ethiopia.

Methods: Facility based retrospective cross-sectional study was conducted at Bule Hora General Hospital involving patients treated during a period of 01 January 2014 to 31 December 2021. Summary statistics such as frequency, mean and percentage were computed and odds ratio calculated. Univariate and multivariate logistic regression were conducted to determine factors associated with poor drug resistant tuberculosis treatment outcomes

Result: Total of 128 participants were involved in the study; the mean age was 34.95 years (±15). Almost half of them, 63 (49.2%) had prior history of TB treatment, and 25 patients (19.5%) had history of drug interruption. Thirty-nine (30.5%) had HIV infection. Drug sensitivity test revealed 3 (2.3%) participants had resistance to rifampicin (RIF), isoniazid (INH), ethambutol (EMB), and streptomycin(SM). All patients received standardized regimens (long- and short-terms standardized regimens), and 74 (57.8%) patients experienced drug adverse effects. Ninety-one (71.1%) participants had favourable outcome defined as cured, 59 (46.09%) and treatment completed, 32 (25%). HIV co- infection (aOR 0.410, 95% CI 0.177-0.973), presence of comorbid medical conditions (aOR 0.206, 95% CI 0.067-0.632), and poor treatment adherence (aOR 0.367 (0.016-8.344) were associated with unfavourable treatment outcome.

Conclusion: The new ambulatory program to manage MDR TB in Bule Hora showed a favourable outcome (71.1%). The outcome of MDR-TB treatment was poor in patients with HIV seropositivity, comorbidities, and a history of drug discontinuation. So this ambulatory program needs to be expanded more in Ethiopia to reduce delay of treatment and patient overload in limited centres.

Key words: MDR-TB, Treatment outcomes, Risk factors, Ethiopia

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ABBREVIATIONS

ART- Anti- Retroviral Treatment

BMI- Body Mass Index

COVID-19 - Corona Virus Disease 2019.

COPD- Chronic Obstructive Pulmonary Disease

DR-TB- Drug Resistant Tuberculosis

EPTB- Extra Pulmonary Tuberculosis

ETM- Ethambutol

HBC- High Burden Countries

HIV- Human immunodeficiency Virus

INH- Isoniazid

MDR-TB - Multidrug resistance Tuberculosis

MTB- Mycobacterial tuberculosis

NICU- Neonatal Intensive Care Unit

OPD- Outpatient Department

RR-TB- Rifampicin Resistant Tuberculosis

SAEs- Severe Adverse Drug Effects

STM- Streptomycin

TIC- Treatment Initiation Centre

WHO- World Health Organization

XDR-TB- Extensively Drug Resistant Tuberculosis

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CHAPTER ONE

1. INTRODUCTION

1.1. Background

Drug-resistant tuberculosis (DR-TB) continues to be a global public health threat (1). World Health Organization(WHO) uses five categories to classify cases of drug resistant tuberculosis as Isoniazid (INH) Resistant TB, Rifampicin Resistant Tuberculosis (RR-TB), Multi-Drug Resistance Tuberculosis (MDR-TB), Pre-Extensive Drug Resistance Tuberculosis (Pre-XDR TB) and Extensive Drug Resistance Tuberculosis (XDR-TB) are used for global surveillance and treatment (1). MDR-TB is Tuberculosis that is resistant to rifampicin and isoniazid; the two most powerful anti-TB medications. Both MDR-TB and RR-TB require treatment with a second-line anti-TB drugs. Pre-Extensive Drug-Resistance (Pre-XDR-TB) is TB that is resistant to rifampicin and any fluoroquinolone (a class of second-line anti-TB drug). Extensively drug-resistant TB (XDR-TB) is TB that is resistant to rifampicin plus any fluoroquinolone plus at least one of the drugs bedaquiline and linezolid (1, 2, 3).

The origin of drug-resistant tuberculosis is mainly the consequence of human mistake as a result of individual or combination of factors related to management of drug supply, patient management, prescription of antimycobacterial medications, and/or patient adherence. The treatment of MDR-TB with second-line drug needs longer duration of treatment, complex and expensive regimens, and is associated with significant adverse drug reaction (4).

After bacteriological confirmation of TB, the detection of MDR/RR-TB requires testing for drug resistance using rapid molecular tests, culture with drug sensitivity test (DST) or sequencing technologies. Treatment requires a course of second-line drugs for a minimum of 9 months to 20 months, which needs a support by counseling and monitoring for adverse drug effects (5).

1.2. Statement of the Problem

Multi-drug resistant TB- is a type of TB that is resistant to at least two of the first-line anti-tuberculosis drugs (Rifampicin and Isoniazid) (6). MDR-TB results from either primary infection with drug resistant strain or may develop in the course of a patient's treatment (7). As MDR-TB patients respond poorly to short course anti-mycobacterial therapy, they need

to be treated aggressively for a minimum of 9 months and up to 20 months with a regimen based on reserve anti TB drugs (1,8).

Worldwide, in 2020, 71% of people with bacteriologically confirmed TB were tested for rifampicin resistance; an increase from 61% in 2019, 51% in 2018. This showed improvements in the coverage of testing for rifampicin resistance in all six WHO regions in 2020. Globally, 157,903 cases of drug resistant-TB were identified and reported in 2020, representing a 22% reduction from 201,997 in 2019 due to COVID-19 pandemic impact on TB care and 150,359 cases of MDR/RR TB were enrolled in treatment in 2020, 15% fall from 177,00 in 2019. Among 30 high TB burden countries (HBC), Eastern European and Western Pacific have the highest number of MDR-TB cases. Nearly 50% of global MDR-TB cases were reported in India (27%), China (14%) and the Russian Federation (8%). WHO Africa region had 2.6% new and 11% retreatment TB cases with MDR-TB. Ethiopia is one of the 30 HBC of MDR TB estimated to achieve 2020 milestone of 20% reduction in TB incidence rate between 2015-2020, and was removed from the list of 30 HBC of MDR-TB from 2021 onwards (1,6).

The rise of multi-drug resistant TB is major threats for the populations of resource-limited countries like Ethiopia in which low socioeconomic status, high burden of infectious diseases and limited access to appropriate healthcare settings worsen the effect of MDR-TB. Furthermore, MDR-TB is more complicated than drug susceptible TB because of poor treatment outcomes, longer treatment time, higher treatment costs (9, 10).

A systematic review and meta-analysis of the prevalence, determinants and treatment outcome of MDR-TB in Ethiopia from 1997 to 2017, analysed in 2018, showed the overall MDR-TB prevalence of 7.24 %; 2.18% among newly diagnosed and 21.07% in previously treated patients (11).

A six-month case–control study performed at different zones of Oromia Region, Ethiopia conducted from 2013–2014 showed that, out of 265 confirmed tuberculosis patients, 33% had laboratory-confirmed MDR-TB (12).

According to cross-sectional community-based study, targeted TB case finding in Mining Sites conducted from December 2015 to June 2016 in Borena and Guji zones, South Ethiopia, the prevalence of MDR-TB was found to be 5.8% (13).

The latest treatment outcome data for people with MDR/RR-TB showed a global treatment success rate of 57% which is even lower than that of WHO 2015 target of 75%. Examples of high MDR-TB burden countries with better treatment success rates (>70%) are Bangladesh, Ethiopia, Kazakhstan and Myanmar (5,6, 14).

According to retrospective descriptive health facility-based study done in Dire Dawa City administration, Dilchora Referal Hospital, Eastern Ethiopia on recorded charts from January 2013 to December 2017, from 146 MDR-TB patients started treatment, 87.7% had favourable outcome, 72.6% patients were cured, 15.1% were completed treatment and 12.3% patients had unfavourable outcome, 8.2% died, 4.1% had treatment failure. Factors associated with poor outcomes were MDR-TB-HIV coinfection and socio-behavioural risk factors like chat chewing, cigarette smoking, alcoholics and drug abusers (15).

However, outcomes of the MDR-TB treatment and associated factors were not described fully in most peripheral treatment initiation centers (TIC) of Ethiopia like Bule Hora General Hospital. Assessing populations receiving a second-line anti-TB chemotherapy, to determine the overall survival rate has a paramount importance for proper planning and effective implementation.

Almost all researches conducted in Ethiopia on MDR-TB treatment outcome and associated factors were undertaken in regional capitals, city administrative, referral hospitals and teaching hospitals which were better equipped with human resources and medical setups. Evidence on MDR-TB treatment outcomes from less well-equipped remote hospitals in Ethiopia, such as Bule Hora General hospital, is almost non-existent. This study has tried to provide an insight on MDR-TB treatment outcomes and associated factors in one of the remote hospitals in Ethiopia.

1.3. Significance of the Study

To the investigator's knowledge, this is the first study of its kind that tried to assess MDR-TB treatment outcome in remove hospital in Ethiopia. The findings in this study will help highlight the gaps in the management of MDR-TB patients at peripheral hospitals and factors associated with unfavorable outcome. It will help care providers and program managers with valuable information to design better approach to improve treatment outcome in MDR-TB patients

CHAPTER TWO

2. LITERATURE REVIEW

Worldwide, in 2020, 71% of people with bacteriologically proven TB were tested for rifampicin resistance, an increase from 61% in 2019 with improvements in the coverage of testing for rifampicin resistance in all six WHO regions in 2020. A global total of 157,903 cases of drug resistant-TB were identified and reported in 2020, representing a 22% reduction from 201,997 in 2019, due to COVID-19 pandemic impact on TB care and 150,359 cases of MDR/RR TB were enrolled in treatment in 2020, 15% fall from 177,00 in 2019, this is also due to the impact of COVID-19 on TB treatment. Ten countries; including China, DR Congo, India, Indonesia, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa and Vietnam accounted for 70% of the global gap between treatment enrolments and the estimated number of new cases of MDR/RR-TB in 2020, and thus will have a strong influence on progress in closing this gap (1).

Among 30 high TB burden countries (HBC), Eastern European and Western Pacific have the highest numbers of cases with MDR-TB, with 21.6% of new cases and 76% of previously treated. Almost 50% of world MDR TB cases were identified in India (27%), China (14%) and the Russian Federation (8%). WHO Africa region had 2.6% new and 11% retreatment TB cases with MDR-TB; Ethiopia is out of 30 HBC of MDR TB from 2021 onward (1,6).

Multi-drug resistant TB is a type of TB that is resistant to at least two of the first line anti-Tuberculosis drugs (Rifampicin and Isoniazid) (1,6). MDR-TB results from either primary infection with drug resistant strain or may develop in the course of a patient's treatment (7). As MDR-TB patients respond poorly to short course anti-mycobacterial therapy, they need to be treated aggressively for a minimum of nine months to 20 months with a regimen based on reserve anti-TB drugs (1,8).

The rise of MDR-TB is a major threat for the populations of resource-limited countries like Ethiopia in which low socioeconomic status of the people, high burden of infectious

diseases and limited access to appropriate health care settings worsen the effect of MDR-TB (9,10). MDR-TB is more complicated disease than drug susceptible TB (9,10).

According to studies conducted in different Asian countries from 2006 to 2015, males dominate MDR-TB cases. Factors associated with presence of MDR-TB were being female (17), cigarette smoking (17), recent contact with TB diagnosed patients (17), previous history of TB treatment (17), HIV co-infection (18,19). The most common type of MDR-TB infection was pulmonary (98%) (19). MDR-TB treatment success rate varies significantly between countries ranging from 43.5% (Armenia and Abkhazia, Georgia) (28), 69.6% (China), (16), and 75% (Pakistan) (20). Predictors of poor treatment outcome among MDR-TB patients were being males (20), rural residency (20), comorbidities (20), age >60 years (16,20), relapsed cases (16), treatment after failure (16), history of drug interruption (28), previous use of second-line anti-TB medications (20) and patients experiencing adverse events (16).

According to case-control study done in Europe, Serbia from September 1, 2009 to June 1, 2014, factors associated with development of MDR TB were low monthly income (less than 100 Euros), defaulting from treatment, stigma associated with tuberculosis, chronic obstructive pulmonary disease (COPD) as comorbidity, use of sedatives and feeling sadness (21).

Studies conducted in African countries from 2013 to 2019 showed that male MDR-TB outnumbered females (22, 23, 24)); mean age at diagnosis was 38.3 years. The majority of MDR-TB patients had previous TB treatment history (82.2%) (22), while others had history of alcohol drinking, cigarette smoking (22). HIV co-infection with MDR-TB was 34.6% in Tanzania (22), 74% in Zimbabwe (29). More than half (51.4%) MDR-TB patients had a BMI below 18kg/m^2 in Tanzania and Uganda (22, 23). Factors associated with outbreak of MDR-TB from Ugandan study were poor adherence to first line anti-TB drugs, and HIV co-infection (24). Treatment success rate of MDR-TB patients were 53.5% (Morocco) (31), 61% (Zimbabwe) (29), 63.5% (Sudan) (33), 71.6%(Uganda) (23), 75.7%(Tanzania) (22). Indicators of unfavourable treatment outcome were male sex (31), mild, moderate, and severe anaemia (23), being co-infected with HIV and ART-naïve (29, 32), unemployment (30), being married (30), smoking cigarettes (22,31), BMI below 18 kg/m^2 (22), rural

residency (33), relapse and previous exposure to second-line anti- TB drugs (23, 33). From all, one quarters to one half developed SAEs such as hearing impairments, psychosis, jaundice, skin rash, electrolyte disturbance and GI upset (29, 32).

According to studies done from 2010 to 2019 in different regions and City administrations of Ethiopia; male predominated MDR-TB patients (12, 25, 26, 27), most patients were urban dwellers (67.6%) (25), median age at diagnosis was 28 years (25,26). More than one third patients (39%) had at least one comorbidity from which HIV co-infection and malnutrition were common (25, 26); more than two third of MDR-TB patients (69%) had BMI less than 18kg/m^2 (25). More than two thirds (71.6-79.53%) MDR-TB patients were previously treated for tuberculosis (26, 27). One quarters (24.2%) of MDR-TB patients in Amhara region were HIV co-infected (26). The overall prevalence of MDR-TB in Ethiopia was 7.24 %, from which 2.18% were newly diagnosed and 21.07% had history of previous treatment (11). MDR-TB was significantly associated with occupation; being a farmer increased the risk of occurrence of MDR-TB (12). Similarly, TB contact history (12), alcohol drinking (12), concurrent disease like HIV/AIDS (12), previous TB history (11, 12), and previous TB treatment were predictors of MDR-TB acquisition (12). Favourable treatment outcome of MDR-TB patients in Ethiopia were 42.2%(37), 59.2%(35), 65.9%(25), 78.6%(36), and (79%)(26). Predictors of unfavourable outcomes were being elderly (25, 34), HIV co-infection (11, 26, 34), underweight (26), malnutrition (BMI < 18.5 kg/m^2) (34), history of anti-TB drug interruption, anaemia (26, 34), EPTB (34), presence of non-HIV comorbidities-43% (34) and hypokalemia as an adverse drug effect (25, 37, 38).

CHAPTER THREE

3. OBJECTIVES

3.1. General objective

- ✓ To assess the treatment outcome and associated factors of MDR-TB patients treated at Bule Hora General Hospital MDR-TB during a period of 01 January 2014 to 31 December 2021.

3.2. Specific objectives

- ✓ To determine treatment outcome of MDR-TB among patients in Bule Hora General Hospital treatment initiation center treated during 01 January 2014 to 31 December 2021.
- ✓ To identify factors associated with MDR-TB treatment outcome among patients treated at Bule Hora General Hospital treatment initiation center during a period of 01 January 2014 to 31 December 2021.

CHAPTER FOUR

4. METHODS AND METERIALS

4.1. Study Area and Period

The study was conducted at Bule Hora General Hospital, which is located in West Guji zone, Bule Hora Town, Oromiya Region, south Ethiopia; 470 km from Finfinnee/Addis Ababa. Bule Hora General Hospital has six wards (Pediatric ward, Neonatal Intensive Care Unit, Obstetrics and Gynecology ward, Surgical ward, Burn Unit, Medical Ward and MDR-TB Center) with about 118 beds. It has four OPDs (Emergency OPD, Dental Clinic, Ophthalmic Clinic and Psychiatry OPD).

Bule Hora General hospital also provides ART services, pharmacy services, ante-natal care service, and delivery service to the nearby community. The hospital was established in 1997 as primary hospital in Bule Hora Town and gives TB service since then and started MDR TB service since 2014.

Study period: The study was carried out from November 2021 to December 2021.

4.2. Study Design

Facility based cross-sectional study was employed. Medical records of 128 patients treated for MDR-TB were scrutinized for necessary information on demographic, clinical parameters, socio-behavioural risk factors and previous TB treatment. Treatment outcomes to MDR-TB therapy, any interruptions in treatment, adverse drug reactions, and laboratory parameters were evaluated from the patient records

4.3. Selection of study participants

4.3.1. Source Population

All forms MDR/RR TB cases at Bule Hora General Hospital were included in the study.

4.3.2. Study Population

All diagnosed MDR-TB patients; enrolled into Bule Hora General Hospital, from 01 January 2014 to 31 December 2021.

4.4. Sample Size Determination and Sampling Procedure

No sample size calculation formula was used for this study, since all MDR-TB patients were included in the study

4.5. Eligibility Criteria

4.5.1. Inclusion criteria

All bacteriologically confirmed and clinically diagnosed MDR-TB patients with known endpoint(outcome) were included.

4.5.2. Exclusion criteria

MDR-TB patients with incomplete records.

MDR-TB patients who were transferred out to the other treatment center

XDR-TB patients at the start of treatment

4.6. Study Variables

4.6.1. Dependent variable

MDR-TB Treatment outcome (favourable vs Unfavourable)

4.6.2. Independent Variables

- **Demographic variables:** Age, sex, place of residency, occupation, educational status
- **Behavioural Variables:** Cigarette smoking**,** khat chewing**,** alcohol drinking
- **Clinical Variables:** Comorbidity**,** Previous TB treatment**,** affected organ/system**,** nutritional status**,** HIV status**,** body mass index (BMI)**,** marital status**,** treatment regimen**,** treatment adherence to anti-TB drugs**,** sputum culture**,** sputum Xpert result, medication adverse effects.

4.7. Data Collection Procedure and Quality

Data collection tool and checklist has been adopted and modified from previous similar studies and guidelines. Pre-test was conducted for 5% of charts to ensure the consistence of the information to be collected. Two professionals with the experience of working at the MDR-TB ward were selected as data collectors and oriented on basic procedures of data collection. Data collection system was closely supervised by the principal investigator to ensure the quality of data. The collected data was checked for completeness.

4.8. Data Processing and Analysis

The data was checked for completeness, coded and entered into Epidata3.1 and exported to SPSS version 25 for analysis. Summary statistics such as frequency, and percentage was computed and odds ratio calculated with 95% confidence interval. Results were expressed in tables and graphs. Bivariate logistic regression model was used to test association between each independent and outcome variables. Variables that showed marginal significance during bivariate analysis at P<0.25 were included in multivariable logistic regression. Variables with statistically significant association at P value of <0.05 with outcome variable were expressed as potential risk factor for MDR TB treatment outcome.

4.10. Operational Definitions

Cure: Defined as patient who completed treatment and at least five final consecutive cultures of his or her sputum during the final 5-12 months of treatment were negative; or if one culture was positive, then at least three of its following consecutive cultures had to be negative

Treatment completed: Defined as patients who had completed their treatments without evidence of failure but with inadequate bacteriologic records to be defined as cure

Treatment failure: Defined when two or more positive sputum cultures of the 5 final cultures, or one positive culture of the final 3 cultures during the final 5-12 months of treatment

Lost to follow-up (default): Defined as patients whose treatment was interrupted for two or more consecutive months against their clinician's advice.

Treatment success: Defined as cure or completed treatment

Poor treatment outcome: Outcome was defined as treatment failure, default or death.

Anemia- Defined as patients with hemoglobin less than 13 g/dl**.**

Clinically diagnosed MDR-TB- Defined as tuberculosis patients diagnosed by Gene-Xpert or AFB and started treatment with first line anti-TB drugs, but not responding to treatment, rifampicin resistance by Gene-Xpert was not detected and culture was not done.

Mulit-drug resistant tuberculosis: Tuberculosis that is resistant for rifampicin by Gene-Xpert and/or other drugs mainly isoniazid by culture and drug sensitivity

4.11. Ethical Considerations

Ethical clearance of the study was obtained from Jimma University Health Science Ethical Review Board. Patient records were encrypted and kept confidential and could only be accessed by hospital staff after obtaining permission from the Bule Hora General Hospital Administration Department.

4.12. Dissemination Plan

The results of the study will be submitted to JUMC department of Internal Medicine, Bule Hora General Hospital, and Oromia Regional Health Bureau. Attempts will be made to present the research findings at scientific conferences and publish the findings in a peer reviewed scientific journal.

CHAPTER FIVE

5. RESULT

5.1. Socio -Demographic Characteristics of participants

A total of 144 medical records of MDR-TB patients who were enrolled to the treatment from 2014 to 2021 were reviewed for this study. Sixteen participants (11.1%) were excluded from data analysis, because eight (5.6%) were still on treatment during the study period, three (2.1%) transferred out to another MDR-TB treatment center and five (3.4%) had incomplete data records. A total of 128 MDR-TB patients with complete medical records were included in this study. Mean age of study participants was 35.0 years (±15). Seventy patients (54.7%) were 14 to 30 years of age, while only 20 (15.6%) were 55 years and older. Eighty (68%) study participants were male. Majority of the participants (69.5%) were married. Majority (89.8%) were Oromos in ethnicity. Majority of the respondents (67.2%) were protestant Christians. Nearly one third (29.7%) participants were unable to read and write and only 11(8.6%) attended diploma and above. More than half, (54.7%) were rural residents. Thirty-seven (28.9%) of the study participants were farmers (Table 1 and 2).

Table 1: Socio demographic characteristics of MDR-TB patient who were on treatment in Bule Hora General Hospital, Oromia, Southern Ethiopia (n=128)

Variables		Frequency	Percentage
Sex	Male	87	68
	Female	41	32
Marital Status			
	Single	30	23.4
	Married	89	69.5
	Widowed	8	6.3
	Divorced	1	0.8
Ethnicity			
	Oromo	115	89.8
	Burji	5	3.9
	Gedeo	3	2.3
	Amhara	5	3.9
Religion			
	Protestant	86	67.2
	Muslim	16	12.5
	Waaqeffataa	14	10.9
	Orthodox	12	9.4
Educational status			

Unable to read and write	38	29.7
Read and write only	31	24.2
Grade 1-8	35	27.4
High school	13	10.2
Higher education	11	8.6
Residence		
Rural	70	54.7
Urban	58	45.3
Occupations		
Government employee	13	10.2
Private sector employee	21	16.4
Daily labourer	10	7.8
House wife	19	14.8
Merchant	11	8.6
Farmer	37	28.9
Others	17	13.3

5.2. Clinical characteristics of MDR-TB patients

The median time from date of diagnosis to treatment initiation was 8 days (IQR=8.5). As shown in Table 2, thirty nine patients (30.5%) were found to be HIV positive at the time of diagnosis, out of which 18 (46.2%) were on HAART. Twenty three HIV infected patients had a CD4 report at the time of diagnosis, out of whom, 43.5% had a CD4 counts greater than 200 cells/dl and 34.8% participants had CD4 count less than 100 cell/dl. Among all participants, 66 patients (51.6%) were newly enrolled. Sixty patients (46.9%) previously received first-line anti-tuberculosis treatment. Half of MDR-TB cases (50.8%), were newly diagnosed TB cases. Only 2 patients (1.6%) had extra pulmonary (lymph node) MDR-TB. All of the study participants were treated with standardized treatment regimen (both long term regimens and short term regimens). Sixteen (12.5%) of the study participants had at least one form of comorbidities other than HIV. The most common comorbid conditions were Diabetes Mellitus 6(31.6%), Hypertension 6(31.6%), and Chronic Liver Disease 4(21%).

After initiation of MDR-TB treatment, 25 (19.5%) of study participants discontinued their treatment. Of these, 64% had poor compliance.

Considering social and behavioural risk factors; 102(79.7%) had no documented social and behavioural risk factors, while 26(20.4%) had at least one socio-behavioral risk factors, out of which majority 13(50%) were alcohol misusers.

The mean BMI was 18.6 Kg/m² (±2.3). From 110 patients with documented BMI, 47(42.7%) of the study participants were malnourished (BMI< 18.5 Kg/m²). All of the study participants had treatment and nutritional support (high protein diet, and plumpy nut). Majority, 124(96.1%) of supporters were NGOs. Seventy four (57.8%) of MDR-TB patients had experienced adverse drug side effect during the course of their treatments. The commonest drug adverse effect patients repeatedly encountered was GI upset 53(71.6%).

Table 2: Clinical characteristics of MDR-TB patients in Bule Hora General Hospital, Oromia, Southern Ethiopia (n=128)

Variables	Frequency	Percentage
HIV status of patients		
Positive	39	30.5
Negative	89	69.5
Treatment status of HIV positives at the time of diagnosis		
New	21	53.8
On HAART	18	46.2
CD4 Count of HIV positives at the time of diagnosis		
<100	8	34.8
100-200	5	21.7
>200	10	43.5
Registration category of MDR-TB patients		
New	66	51.6
Relapse	48	37.5
After lost to follow-up	1	0.8
After failure of first treatment	12	9.4
After failure of retreatment	1	0.8
History of previous TB treatment		
New	65	50.8
Treated with first line	60	46.9
Treated with second line	3	2.3
Site of MDR-TB		
Pulmonary TB	125	97.7
Extra pulmonary TB	2	1.6
Disseminated TB	1	0.8
Treatment regimens		
Standard regimens	128	100
Presence of comorbidity		
No comorbidity	109	85.2
Comorbidity present	19	14.8
Hypertension	6	31.6
Diabetes Mellitus	6	31.6

Chronic Liver Disease	4	21
Others	3	15.8
History drug interruption		
Yes	25	19.5
No	103	80.5
The reasons for drug interruption		
Adverse drug effect	9	36
Poor adherence	16	64
Socio-behavioural risk factors		
None	102	79.7
Alcohol misuse	13	10.2
Smoking	5	3.9
Khat chewing	8	6.3
Anthropometric Measurement		
BMI	Mean=18.6kg/m2±2.3	
<18.5Kg/m2	47	42.7
18.5-25kg/m2	62	56.4
>25 kg/m2	1	0.9
Having treatment and nutritional support		
Yes	128	100
No	0	
Who give nutritional support?		
Government	4	3.1
NGOs	124	96.9
Family	50	39
Drug adverse effects		
Yes	74	57.8
No	54	42.2
Types of drug adverse effects		
Hepatitis/jaundice	10	13.5
GI Upset	53	71.6
Renal toxicity	5	6.8
Psychiatric illness	2	2.7
Ototoxicity	1	1.4
Others	1	1.4

HIV- human immunodeficiency virus; HAART-highly active anti-retroviral therapy; NGOs- Non government organizations; GI- Gastrointestinal

5.2.1. Laboratory Characteristics of MDR-TB Patients

Majority of MDR-TB cases were initially diagnosed by GeneXpert, 112(87.5%); others were diagnosed clinically. Culture was sent to central Laboratory for all patients with sputum production, as soon as diagnosis was made by Gen-Xpert and clinically, as a baseline. Baseline

smear also was done for patients with productive cough. More than half, 69(53.9%) of the study participants had positive smear result before initiation of treatment. Majority, 86(67.2%), of the study participants had positive baseline culture at initiation of treatment. Here some patient's culture result did not return from central laboratory and some were diagnosed with Gene X-pert only. Concerning drug and sensitivity pattern, 112(87.5%) of the study participant had RIF resistance (including RIF detected by both Gene-Xpert and culture), about 13 (10.2%) had resistance for both RIF and INH and 3(2.3%) had resistance to RIF, INH, EMB and SM. Mean hemoglobin level of study participants were 12.9g/dl (±2). From 81 study participants for whom HGB was documented, 26(32%) patients had anemia, from which majority, 18(69.2%) had mild anemia (Hgb 11-12 g/dl), 7(27%) had moderate anemia (Hgb 9-10 g/dl) and 1(3.8%) had severe anemia (Hgb<8g/dl).

Table 3: Laboratory characteristics of MDR-TB patients in Bule Hora General Hospital, Oromia, Southern Ethiopia (n=128)

Variables	Frequency	Percentage
Smear status of clients at baseline		
Positive	69	53.9
Negative	9	7
Unknown	50	39.1
Results of culture at baseline		
Positive	86	67.2
Negative	4	3.1
Unknown	38	29.7
Drug sensitivity result at baseline		
RIF Resistance only	112	87.5
Resistance to RIF and INH	13	10.2
Resistance to RIF, INH, EMB, SM	3	2.3
Hemoglobin Categories of Clients		
≤8 g/dl	1	1.2
9-10 g/dl	7	8.6
11-12 g/dl	18	22.2
≥13 g/dl	55	67.9

5.2.2. Treatment outcomes of MDR-TB patients at Bule Hora hospital

As displayed in the figure 1 below, 91(71.1%) of the study participants had favourable outcome. Fifty nine (46.09%) were cured, and 32(25%) were completed treatment. Thirty seven (28.9%) had unfavourable outcome from which 31(24.2%) were died, 5(3.9%) and 1(0.8%) were treatment failed.

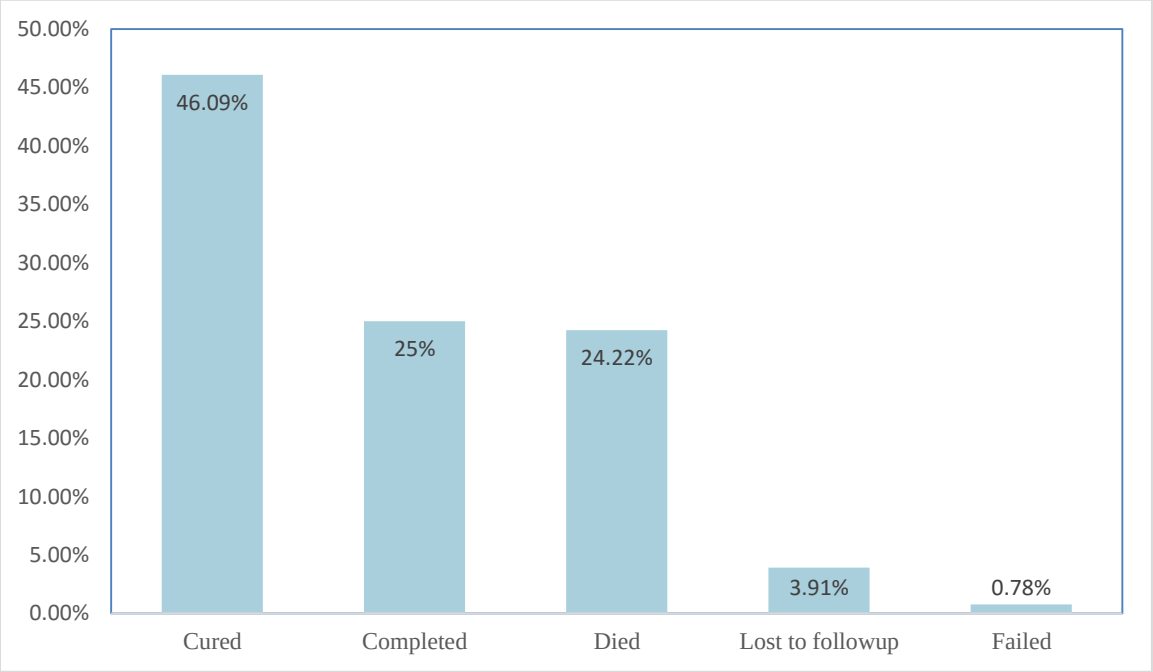

Figure 1: Treatment outcome of MDR-TB patients who were on treatment in Bule Hora General Hospital, Oromia, south Ethiopia (n=128).

5.2.3 Bivariate and Multivariate Analysis

On bivariate analysis of the dependent and independent variables, presence of comorbidities, presence of at least one socio-behavioural risk factor (such as alcohol misuse, smoking and khat chewing), and history of drug interruption were found to have significant association with unfavourable treatment outcome ($p \leq 0.05$).

When adjusted on multivariate analysis, TB/HIV co-infection (aOR 0.415, 95%CI 0.177-0.973; p-value 0.043), presence of comorbidity (aOR 0.206, 95%CI 0.067-0.631; P-value 0.018) and history of drug interruption (aOR 0.367, 95%CI 0.016-0.834; P-value 0.011) were statistically significantly associated with poor treatment outcome (table-4).

Thus, HIV co-infected MDR-TB patients, presence of comorbidities with MDR-TB patients, and history of anti-TB drugs interruption were associated with unfavourable treatment outcome. Those TB/HIV co-infected patients were 73.7% less likely had favourable treatment outcome than non HIV co-infected MDR-TB patients. Similarly patients who had comorbidities were 92.3% less likely had favourable treatment outcome than MDR-TB patients who had no

comorbidity. MDR-TB patients with history of anti-TB drug interruption had 85.7% less likely had favourable treatment outcome as compared with those without history of drug interruption.

Table 4: Bivariate and multivariate analysis of factors associated with treatment outcome among MDR-TB patients in Bule Hora General Hospital, Oromia, Southern Ethiopia (n=128)

Variables	Favorable outcome		Total	COR (95% CI)	AOR (95% CI)	P- value
	YES	NO				
HIV/TB						
Yes	24(26.3%)	15(40.5%)	39(30.5%)	0.525(0.135-1.175)	0.415(0.177-0.973)	**0.043**
No	67(73.7%)	22(59.5%)	89(69.5%)	1	1	
CD4 Count						
<200	4(36.4%)	9(75%)	13(56.5%)	0.190(0.032-1.145)	0.057(0.002-1.348)	0.076
≥200	7(63.6%)	3(25%)	10(43.5%)	1	1	
Comorbidity						
Comorbidity other than HIV	7(7.7%)	9(24.3%)	16(12.5%)	0.259(0.088-0.761)	0.206(0.067-0.632)	**0.018**
No comorbidity	84(92.3%)	28(75.7%)	112((87.5%)	1	1	
History of drug interruption						
Yes	13(14.3%)	12(32.4%)	25(19.5%)	0.347(0.141-0.858)	0.367(0.016-8.344)	**0.011**
No	78(85.7%)	25(67.6%)	103(80.5%)	1	1	
Socio-behavioral risk factors						
At least one risk factor present	14(15.4%)	12(32.4%)	26(20.3%)	0.379(0.155-0.925)	4.816(0.125-185.760)	0.166
No risk factors present	77(84.6%)	25(67.6%)	102(79.7%)	1	1	
HGB(g/dl)						
<12.9	23(35.4%)	16(55.2%)	39(41.5%)	0.445(0.183-1.085)	0.230(0.013-4.047)	0.090
>13	42(64.6%)	13(44.8%)	55(58.5%)	1	1	
History of TB treatment						
New	50(54.9%)	15(40.5%)	65((50.8%)	1.789(0.824-3.884)	0.339(0.019-6.013)	0.110
Ever treated	41(45.1%)	22(59.5%)	63(49.2%)	1	1	

CHAPTER SIX

6. DISCUSSION

We found that the overall treatment success (i.e. having an outcome of cured or treatment completed) at the end of the treatment (9 to 24 months) was 71.1% (95% CI), which is in accordance with the WHO report of Africa region (69%) (1). This is similar with other resource limited countries such as Pakistan 75%% (20), Tanzania 75.7% (22) and Uganda 71.6% (23). The favourable outcome is lower than the treatment outcomes reported from inpatient model of care in Addis Ababa at St Peter Hospital in 2015(78.6%) (35) and health facility-based study of Dire Dawa City Administration at Dilchora referral hospital, Eastern Ethiopia in 2018(87.7%) (15). There are many possible explanations for this difference in outcome from similar studies in Ethiopia. One reason is the setup, as Bule Hora is one of remote center from capital, Addis Ababa and more rural when compared with Dire Dawa City Administration, one of the two city administration in Ethiopia. Bule Hora Hospital has insufficient man power and materials to care for MDR-TB patients and treatment related complications which may have significant effect on treatment outcome. The treatment center was new with new ambulatory model of care, clients had a substantial HIV-coinfection rate and malnutrition (BMI<18.5). Yet, the outcome in our study is better than reports from other low resource settings and middle income countries such as Morocco 53.5% (31), Sudan 63.5% (33) and Zimbabwe 61% [29].

The other reasons for better outcome in our study could also be due to reasons related to the study population and the treatment program. The clients in this study were generally young with mean age of 34.95 years (±15). In addition, patients were started treatment as outpatient ambulatory model of care and followed at treatment initiation center during the first month of treatment and received directly observed therapy at various treatment follow-up center. 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 for nutritional support mainly by NGOs.

This study had higher rate of unfavorable treatment outcome, death (24.2%), compared with study in patients who began treatment as inpatients in Addis Ababa in 2015(13.9%) (36). The

possible explanations for high death rate in our study could be due to limitations of the facility itself that, in turn, is due to inadequate man power and unsatisfactory facility to care adequately for patients. Secondly, a diagnosis of MDR-TB in Bule Hora setup is mainly by GeneXpert, and culture and DST tests sent to central laboratory did not return to treatment center. As a result, identification of specific drug resistance was impossible without culture except in rifampicin and these may affect outcome adversely. Thirdly, late diagnosis of MDR-TB might be responsible, as the majority of our patients were treated with first-line anti tuberculosis (46.9%). This finding suggested that for further improvement of the treatment outcome, early diagnosis of drug-resistant TB is paramount importance. Effective treatment need to be started as early as possible before the patients' compliance decline as a result of fatigue with the first-line anti-TB drug treatment. Fourth, Bule Hora is the only center in Southern Oromia, including Burji Special Wereda, and part of Gedeo district of Ethiopia's SNNP region, and the lack of adequate health care coverage may delay the diagnosis and treatment.

Since MDR-TB was first reported, HIV co-infection has been associated with poor treatment outcomes in MDR-TB patients (11, 26, 28, 31, 33). In our study, regardless of CD4 cell count, unfavourable treatment outcome was statistically significantly associated with HIV co-infection. Treatment success rate (26.3%) among HIV coinfected patients, and unfavourable outcome (40.5%) were almost similar to study done in Zimbabwe (39.3%) (29) and Tanzania (38.8%) (22). However, it is higher than that of St. Peter's Hospital, Addis Ababa, Ethiopia (20.3%) (36). This could have been due to unknown HIV sero-status of clients before diagnosis of MDR-TB in our study. So patients presented lately with advanced stage of HIV and delay in use of ART drugs, since more than half (53.8%) HIV positive patients in our study were new to HAART.

Patients with history of drug interruption had unfavourable treatment outcome in this study when compared with treatment non-interrupters (32.4% vs 14.3%). There was significant association of drug interruption and unfavourable treatment outcome in the study done in Armenia and Abkhazia Georgia (56.5%) (28), higher than our finding, which could be explained by the study in Armenia and Abkhazia Georgia was mainly assessed for drug interruption and outcome. However, in our study, many other variables were assessed for association with the outcomes. Study done in Ethiopia also showed significant association of at least one history of anti-TB drug interruption and unfavourable MDR-TB treatment outcome when compared with no history of drug interruption (41.7% vs 22.2%); this is almost comparable with our finding (38).

The presence of comorbidity other than HIV was the other factor that was significantly associated with unfavourable treatment outcome in this study when compared with patients without comorbidities (24.3% vs 7.7%) with P -0.018. The study done in Uzbekistan showed an association of comorbidities and unfavourable treatment outcome among MDR-TB patients when compared with patients without comorbidities, assessed for each cardiovascular, liver disease and diabetes mellitus (63% vs 42.4%, 72.7% vs 41.9%, 65% vs 43.6% respectively) (39). The finding was higher than our finding, because, it was done for individual comorbidities association. There were significant association of presence of comorbidity other than HIV and poor treatment outcomes according to meta-analysis done Ethiopia, almost comparable to our findings (29.5%) (34). A fundamental aspect of the program presented here was the implementation of adherence strategies successfully employed in the ambulatory program; monthly patient visits to the treatment initiation site's OPD, identification of a patient supporter to assist with DOT, psychosocial support, monthly food baskets and social support for the patients who have no family supporter.

Adverse drug effects in this study were encountered in more than half patients, with gastrointestinal toxicity, hepatitis/jaundice, renal toxicity, and psychiatric illness as the most frequent adverse drug effects though these are not statistically associated with the treatment outcome in contrast with reports from other MDR TB treatment outcome and associated factors studies elsewhere (11,25). This may be due to incomplete documentation of the severity of the side effects from the retrospective records that we used and lack of investigations or documentation of serum electrolytes and incomplete documentation of blood counts, liver function tests and renal function tests.

Conclusion and Recommendations

This ambulatory program to manage MDR TB in Bule Hora showed a more or less favorable outcome, amid large resource constraints and with a substantial HIV co-infection burden. The outcome of MDR-TB treatment was poor in patients with HIV seropositive, history of anti-TB drug interruption and those who had comorbidity. HIV screening should be reemphasized among MDR-TB patients for early initiation of ARTs. In order to prove the association between the outcome of MDR-TB treatment and history of anti-TB drug interruption, larger scaled researches may be needed.

Limitations

All the data for necessary variables could not be obtained fully and the reliability of the data may not be ascertain because it is retrospective study and based on records. Adverse drug effects could not be analyzed by MDR-TB regimen properly due to limited biochemical findings in the study area. Small sample size might have limited the statistical power of the study.

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Annex 1: Data collection tool (checklist):

This checklist is prepared to assess MDR-TB treatment outcome and factors associated with unfavorable treatment outcome.

Part I: Checklist for socio demographic characteristics of the patient:

Patient's unique MDR-TB registration no. =……...

No	Questions	Response
1	Sex	1, Male 2, Female
2	Age	……in years
3	Educational status	1, Unable to read and write 2, Read and write only 3, Grade 1-4 4, Grade 5-8 5, Grade 9-12 6, Colleges, Universities
4	Marital Status	1, Single 2, Married 3, Widowed 4, Divorced(legally)
5	Religion	1. Muslim 2. Orthodox 3. Protestant 4. Catholic 5. Waaqeffataa/ttu 6. Others(specify)

6	Ethnicity	1. Oromo 2. Amhara 3. Burji 4. Gedeo 5 Others (specify……)
7	Occupation	1. Government employee 2. Private sector employee 3. Farmer 4. Daily laborer 5. House maid/servant 6. Merchant 7. Others (specify…….._____
8	Residence	1. Urban 2. Rural
9	Monthly income	……..write in ETB

Part II. Checklist for clinical characteristics of patient:

1. Time from diagnosis to treatment initiation of MDR-TB
    1. Date of diagnosis……. /……./……..
    2. Date of treatment initiation……/……. /…….
    3. Delay of treatment initiation……. days
    4. Date of treatment completion……/……. /……
2. HIV status of the patient
    1. Positive 2. Negative 3. None
3. If HIV positive, what was the treatment status of HIV at the diagnosis of HIV
    1. New 2. On HAART
4. If HIV positive, what is the CD4 count at the time of MDR-TB diagnosis?
    1. Number (…….) 2. Percentage (%)……..
5. Registration category of MDR-TB patient:
        1. New

2. Relapse

3. After lost to follow up

4. After failure of first treatment

5. After failure of retreatment

6. Other, specify……

6. History of previous TB treatment

1. New
2. Treated with first line
3. Treated with second line

7. Site of MDR-TB

1. Pulmonary TB
2. Extra-pulmonary T
3. Disseminated TB

8. MDR-TB patient's treatment regimens (specify the regimen code in front of the choice)

1. Standard regimen……
2. Individualized regimen……..
3. Empirical treatment…….

9. Presence of comorbidities

1. COPD
2. DM
3. HTN
4. Chronic renal disease
5. Chronic liver disease
6. Others/specify……
7. None

10. History of drug interruption

1. Yes
2. No

11. If yes to question number 10, what was the reason for interruption?

1. Failure
2. Adverse drug effect
3. Drug stock out
4. Poor adherence
5. Others (specify…..)

12. Patients social/behavioral risk factors(more than one response-possible)

1. Homelessness
2. Drug abuse
3. Alcohol misuse
4. Smoking
5. Khat chewing
6. Others (specify……)
7. None

13. Anthropometric measurement of the patient at the start of treatment

1. MUAC…….cm 2. Weight ……Kg 3. BMI…….kg/m2

14. Does the patient have treatment and nutritional support?

1. Yes 2. No

15. If 'yes' to 14, who give the support?

1. Family member
2. Government
3. NGO
4. Others (specify……)
5. None

16. Did the patient develop adverse drug side effect?

1. Yes 2. No

17. If yes to question 16, what was the side effect and how frequent?

(Write frequency in number in front of the system affected)

1. Hepatitis (jaundice)……..
2. GI upset ……..
3. Renal toxicities ……
4. Psychiatric illness…….
5. Ototoxicity……..
6. Severe hypokalemia……
7. Others (specify)…

Part III. Checklist for laboratory characteristics of patient:

1. Smear grading at base line

1. 3+
2. 2+
3. 1+
4. Scanty
5. Negative

2. Results of baseline culture

1) Positive 2) Negative 3) Unknown

3. Baseline DST result

1) RIF resistance only 2) Resistance to RIF,INH

3) Resistance to RIF,INH,EMB,SM 4) Others (specify…..)

4. Date of the first culture conversion after treatment initiation (fill the month at which the culture or smear converted to negative)…….

	Basic Laboratories	Value at baseline	At 3 months	At 6 months
5	Hemoglobin(g/dl)			
6	WBC/µL			
7	Serum Creatinine(mg/dl)			
8	Serum BUN(mg/dl)			
9	Serum ALT(U/L)			
10	Serum AST(U/L)			
11	Serum ALP(U/L)			
12	Serum Potasium(meq/l)			

13. What was the final treatment outcome of the patient?

1) Cured 2) Completed 3) Failed

4) Died 5) Lost to follow up

14. Date of treatment outcome_____

15. Duration on treatment in months…….