
# TREATMENT OUT COME OF DRUG-RESISTANT TUBERCULOSIS AND ASSOCIATED FACTORS AT ST. PETER SPECIALIZED HOSPITAL ADDIS ABABA, ETHIOPIA.

**By: - MEKDELAWIT ABEBE (BSc)**

A THESIS SUBMITTED TO THE CDT-AFRICA, COLLEDGE OF HEALTH SCIENCES , ADDIS ABABA UNIVERSITY IN FULFILLMENT OF THE REQUIREMENTS FOR A MASTERS DEGREE IN CLINICAL TRIALS.

**ADVISOR(S):**

**PROFESSOR ASRAT HAILU**

**DR. YIMTUBEZENASH WOLDEAMANUEL**

**August, 2021**

# Table of contents

# List of Tables

## Acknowledgements

First of all, I would like to thank almighty God. Secondly, my heartfelt gratitude goes to CDT Africa, Addis Ababa University, College of Health Sciences, for giving me this opportunity to study this master's program. I would also like to express my special appreciation to my advisors Professor Asrat Hailu and Dr.Yimtubezenash Woldeamanuel for their unlimited advice, constructive suggestions and motivation that helped me. I would also like to thank Dr. Tsegahun Manyazewal for his constructive suggestions. And I would like to give my sincere gratitude to all St Peter Hospital staff. Lastly, my appreciation extends to my colleagues and classmates for sharing their ideas and information.

# Abbreviations/Acronyms

**AAU**: Addis Ababa University

**AFB**: Acid-Fast Bacilli

**AIDS**: Acute Immune Deficiency Syndrome

**AOR**: Adjusted Odds Ratio

**BMI**: Body Mass Index

**CI**: Confidence Interval

**DR-TB**: Drug-Resistant Tuberculosis

**DST**: Drug Susceptibility Test

**HIV**: Human Immunodeficiency Virus

**INH**: Isoniazid

**LPA**: Line Probe Assay

**LTFU:** Lost To Follow Up

**MDR-TB**: Multi Drug Resistant Tuberculosis

**OR**: Odds Ratio

**RIF**: Rifampicin

**RR-TB:** Rifampicin Resistant Tuberculosis

**PI**: Principal Investigator

**SLD**: Second Line Drug

**SPSS**: Statically Package for Social Sciences

**SSA**: Sub Saharan African

**TB**: Tuberculosis

**WHO**: World Health Organization

# ABSTRACT

**INTRODUCTION:**Drug Resistant Tuberculosis is defined as tuberculosis that does not respond to antituberculosis agent. Data on the outcome of MDR/RR-TB and associated factors is highly needed to evaluate the efficiencies of the MDR/ RR-TB treatment program. However, The treatment outcome of MDR/RR-TB at St. Peter Specialized Hospital is not studied.

**OBJECTIVE**: To assess treatment outcomes of MDR/RR-TB and its associated factors at St. Peter Specialized Hospital, Addis Ababa, Ethiopia from 2015 to 2020.

**METHODS**: A retrospective study was conducted among patients treated for drug-resistant tuberculosis from January 2015 - December 2020 at St. Peter specialized hospital. This study included 335 patients treated for multidrug resistant or rifampicine-resistant tuberculosis. The main outcome variable was overall MDR/RR-TB treatment outcome classified as successful and poor. Data were collected by trained nurses. Data entry and analysis were performed using Excel and SPSS. The relationship between MDR/RR-TB treatment outcome and associated factors was evaluated by fitting logistic regression. The final multivariable logistic regression model was a good fit for the data and had no multicollinearity issue. Statistical significance was considered at $p<0.05$.

**RESULTS**: Treatment success was achieved in 71.3% of the patients. The adjusted odds of poor treatment outcome were twice higher in those who had a habit of frequent alcohol drinking (AOR=2.07, p=0.039). Likewise, the adjusted odds of poor treatment outcome was more than 2-folds higher in patients who had a positive result for HIV test. Concerning mortality, the likelihood of death was found to increase by 5% as age advances by one year (AOR=1.05, $p<0.001$). In addition, the risk of death was more than 3-fold higher among MDR/RR-TB patients co-infected with HIV (AOR=3.81, $p<0.001$).

**CONCLUSION:** In this study, the overall treatment success was consistent with studies carried out in different regions of Ethiopia. Again, a higher danger of poor treatment outcome and death was observed among people who drink alcohol, co-infected with HIV/AIDS, and the elderly.Patents with MDR/RR-TB patients, use alcohol and are co-infected with HIV/AIDS should be given greater attention during therapy. More studies should be done to generate data on the factors affecting the treatment of MDR/RR-TB patients to improve the outcome of treatment.

**Key Words**: MDR-TB, RR-TB ,Tuberculosis, Drug Resistance, Outcome

# 1. INTRODUCTION

## 1.1 BACK GROUND

Mycobacterium tuberculosis is one of the species in the family Mycobacteriaceae that is the causative agent of tuberculosis (TB), first discovered in 1882 by Robert Koch. It is transmitted mainly by respiratory droplets through the air during inhalation and primarily affects the lungs (pulmonary TB) but it can also affect any organ of the body(1). Globally TB remains a major cause of death, with drug-resistant forms resurging over the past two decades. Tuberculosis can be effectively treated with first-line drugs (Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) for six months(1). MDR TB is a type of TB that is resistant to the two most effective first-line anti-TB drugs; rifampicin and isoniazid. MDR/RR-TB is mainly attributable to human errors that predispose to drug resistance development, although genetic factors are believed to contribute to a certain extent (2).

Globally, an estimated 10.0 million (range, 8.9-11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years. Drug-resistant TB continues to be a public threat. Increasing prevalence of Multi-Drug Resistance or Rifampicin Resistance tuberculosis (MDR/RR-TB) represents a global public health emergency. Worldwide in 2019, close to half a million people developed rifampicin-resistant TB of which 78% had multidrug-resistant TB. The three countries with the largest share of the global burden were India (27%), China (14%), and Russia (8%)(3).

Treatment provision for MDR/RR-TB has been scaled up over the past decade in Sub-Saharan Africa(SSA). This treatment gap reflects a range of interconnected issues including the complexity of MDR/RR-TB, which includes long treatment duration (24 months) with large numbers of pills taken daily, invasive daily intramuscular injections, side effects due to drug toxicity, and complexities of the clinical management of the co-infection. This results in high mortalities and poor treatment outcomes, a phenomenon that has been described as the "perfect storm". As a result of these complexities, there is a range of potential treatment outcomes, and these are usually classified as cure, treatment completed, death, treatment default, treatment failure, and treatment success(4).

The number of MDR/RR-TB patients enrolled globally for treatment was 139,000 in 2017, equivalent to about 25% of the estimated number of new MDR/RR -TB cases emerging that year alone. Enrolments have increased over time and in several countries.The gap between detecting MDR/RR-TB cases and starting them on treatment has narrowed. Treatment outcomes for MDR/RR-TB cases are poorer compared to drug-susceptible TB cases. This is due to medications used in the treatment of MDR-TB which are less effective and associated with a greater number of side effects, also, treatment duration is at least 20 months which can compromise adherence. Only 55% of the MDR TB patients enrolled who started treatment globally in 2015 were successfully treated, while 15% of patients died and treatment failed in 8% of patients (21% were lost to follow-up or not evaluated)(5).

According to the Ethiopian national TB drug resistance surveillance Ethiopia ranked 15th with new cases of MDR/RR -TB each year and is one of the 27 countries with a high MDR/RR-TB burden. Among 9 million TB patients, an estimated 13% were HIV- positive. African countriesaccounted for 78% of HIV-positive TB cases(6).

The HIV pandemic presents a significant challenge to global tuberculosis control. People living with this disease have a 5% risk of developing MDR/RR-TB. In a presentation at the physician Research network, it is reported that more than half of MDR cases in many SSA countries are HIV-infected persons and that the AIDS epidemic has caused a marked acceleration of the TB epidemic worldwide particularly in Africa(7).

## 1.2 STATEMENT OF THE PROBLEM

Tuberculosis is one of the world's deadliest communicable diseases with most cases in Asia and Africa, including Ethiopia (3-5). The emergence of multidrug-resistant TB is a challenge for the global control and prevention of the disease(6)

The emergence of MDR/RR-TB is a threat for the populations of resource-limited countries. The low socioeconomic status of the people, high prevalence of infectious diseases, and limited access to well-equipped health care facilities worsen the effect of MDR/RR-TB. Furthermore, poor treatment outcomes, longer treatment time (about two years), higher treatment costs, and many more complications make MDR/RR-TB a more complex disease than TB(8).

TB is the major cause of death among people living with HIV and HIV is the main reason for the failure to meet TB control targets in many settings(7). There is evidence that TB patients living with HIV are at a greater risk of harboring and acquiring MDR/RR-TB strains and that HIV-related immunodeficiency is a risk factor for poor outcomes in MDR/RR -TB patients. Ethiopia is the 27 high MDR- TB burden countries with an estimated 2700 (1700–3700) MDR/RR-TB cases among annually notified TB cases. Ethiopia is one of the countries with the highest MDR-TB burdens, with 2.3% of newly confirmed TB patients affected and 17.8% of previously treated TB patients affected(9).

MDR/RR-TB is a serious public health problem in Ethiopia. Previous studies showed that the treatment outcome of MDR/RR -TB in Ethiopia is still a concern. In Ethiopia treatment success among MDR/RR-TB is lower than the acceptable range.Sociodemographic, access to well-resourced healthcare facilities worsens the effect of MDR/RR-TB. Further, higher treatment costs, longer treatment time, poor treatment outcomes make MDR/RR-TB one of the biggest public health challenge. This causes an additional burden on the health system of the country.

Improving MDR-TB treatment outcomes is one of the five priority actions recommended by WHO to address the global MDR-TB crisis , with a target of 75% treatment success by the end of 2015.Many countries currently fall short of this ambitious target.

Data on the outcome of MDR/RR-TB and associated factors is highly needed to evaluate the efficiencies/deficiencies of the MDR/RR-TB treatment program. The treatment outcome of MDR/RR-TB at St. Peter Specialized Hospital, Addis Ababa, Ethiopia has not been studied. Therefore, this study aimed to assess treatment outcomes of MDR/RR-TB and to identify its associated factors at St. Peter Specialized Hospital, Addis Ababa, Ethiopia.

## 1.3 SIGNIFICANCE OF THE STUDY

Assessing the treatment outcome will help to evaluate the MDR/RR-TB program and identify determinants of treatment outcome. These may help the institute as well as the healthcare system for future improvement of treatment care. Given this, the study will provide significant input to policymakers and program managers in Ethiopia to improve MDR/RR -TB treatment policies and strategies and will also in the long term benefit the patients.

# 2. LITERATURE REVIEW

In Ethiopia, the programmatic management of multidrug-resistant/rifampicine resistant tuberculosis (MDR/RR-TB) is entirely based on a WHO recommended long-termtreatment regimen lasting 18 – 24 months. However, growing evidence shows that low treatment success rate and high rates of adverse events are associated with this regimen (10). According to national guideline, MDR-TB/RR should be detected early and treated promptly.MDR-TB/RR diagnosis also must be confirmed for the core first line medicines, rifampicin (R) and isoniazid (H) using rapid molecular drug-susceptibility test (DST) techniques, to initiate treatment. All confirmed MDR/RR-TB pulmonary TB patients again must have baseline screening DST for the coresecond line medicines(fluoroquinolones (FQ)) and second-line injectables (SLI). DST can be performed using the second-line Line Probe Assay (SL-LPA). SL-LPA is performed directly from the sputum specimen collected before or within 7 days of treatment initiation. For MDR/RR -TB patients with documented HIV co-infection, antiretroviral therapy (ART) also should be initiated once anti-tuberculosis treatment is tolerated, preferably within 2 to 8 weeks period. MDR-TB patients living with HIV who have severe immunosuppression (e.g. with CD4 cell count<50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment (11).

## 2.1. Treatment outcome of MDR/RR TB

Multidrug-Resistant Tuberculosis (MDR-TB) is caused by resistance to isoniazid and rifampicin and remains a public health crisis and a health security threat(9). Currently, the emergence of drug-resistant strains of TB is considered a global threat to the control of TB. According to the 2017 report of the World Health Organization (WHO), about 600,000 people were diagnosed with drug-resistant tuberculosis (DR-TB). Globally in 2016, an estimated 4.1% of new cases and 19% of previously treated cases had DR-TB, respectively. In Africa, about 2.7 and 14% of new and previously treated cases were diagnosed with DR-TB, respectively(12).

In Vietnam, a study was conducted among a cohort of 1380 MDR-TB patients enrolled for treatment from January 2010 to December 2012. According to this study, 1008/1380 (73%) had a successful treatment outcome,and 835/1380 (61%) were cured while 173 (12%) had completed treatment. In this report, those with poor outcomes were 372/1380 (27%); out of which, 85/1380

(6%) failed, 111/1380 (8%) died, 174/1380 (13%) were lost to follow-up (LTFU), and 2/1380 (<1%) were transferred out (13).

Another study carried out in Zhejiang province, China, 2009-2013 among 537 MDR-TB patients with known treatment outcomes showed that the treatment success rate was 40.2 per 100 person-years. The number of patients with success, failure, death, and default outcomes was 374/537 (69.6%), 101/537 (18.8%), 36/537 (6.7%), and 26/537 (4.8%), respectively. The success rate of relapsed patients (65.3%) was lower than patients registered as receiving treatment after failure which is 71% (14).

In another study carried out in Pakistan among 181 patients for whom treatment outcome was available, 135/181 (74.6%) were cured, 1/181 (0.6%) completed treatment, 35/181 (19.3%) died, 8/181 (4.4%) failed treatment and 2/181 (1.1%) defaulted (15).

According to a systemic review and meta-analysis study of published works from 3 sub-Saharan Africa (SSA) countries (i.e., South Africa, Lesotho, and Botswana) which collected data from 3368 MDR-TB patients co-infected with HIV, cure and death rates respectively were 34.9% and 18.1%. This study also revealed that MDR-TB and HIV co-infected patients were less likely to be successfully treated than HIV negative MDR-TB patients(risk ratio=0.87, 95%CI 0.97-0.96) (16).

According to a study carried out in Gauteng, South Africa on the clinical outcome of 351 MDR-TB patients composed of 54 (47.5%) females and 170(52.5%) males, successful treatment outcomes were observed for 158/351 (48.8%) of the participants. The rest 93/351 (28.7%) defaulted, 65/351 (20%) died, and 8/351 (2.5%) had treatment failure (17).

A study carried out at Jimma University showed that from 79 re-treatment cases enrolled in the study, 60.8% of them were males. Most (84.4%) of the participants were in the age group of 15-44 years. Of these, 46.8% had a relapse, 43% were treatment failures and 10.1% were defaulters (18).

In another study carried out in Ethiopia from February 2009 to December 2014, a total of 1044 patients were initiated on second-line drugs (SLD). Of these, 612 patients with confirmed or presumed MDR TB had ≥24 months of follow-up, 551 (90.0%) were confirmed, 61 (10.0%)

were suspected MDR TB cases while 603 (98.5%) had prior TB treatment, and 133 (21.7%) were HIV co-infected. Composite treatment success was 78.6% with 396 (64.7%) cured, 85 (13.9%) who completed treatment, 10 (1.6%) who failed, 85 (13.9%) who died and 36 (5.9%) who were lost to follow-up(12).

According to a systematic review study carried out in Ethiopia between 1997 and 2017, involving a total of 7461 MDR-TB patients, 2.18%(95%CI 1.44-2.92%) were newly diagnosed and 21.07%(95% CI 11.47-30.67%) were previously treated for TB. Of these, 8.4-13.9% of the MDR-TB patients died during treatment, 25-64.7% were cured, and 10-16.9% have completed treatment (19).

Another systemic review study carried out in Ethiopia, which reviewed data of 1993 MDR-TB patients revealed that 1288 and 442 patients respectively had a successful and poor treatment outcome. In the pooled analysis, treatment success was observed in 59.2% (95%, CI, 48.1-70.4) of patients, while 23.3% (95%CI, 19.7-27.0) of patients had a poor outcome. In a sub-group analysis, 46.1% were cured, 12.8% treatment complicated, 14.3% have died, 7.5% lost in follow up and 1.6% had treatment failure(10).

## 2.2. Determinants of Treatment outcome among MDR/RR TB patients

In a study carried out in Pakistan, predictors of unsuccessful treatment outcome (death, failure and default) were age >40 years (OR 3.412, $P = 0.009$), baseline body weight <40 kg (OR 2.966, $P = 0.020$), and concurrent comorbidity (OR 3.785, $P = 0.023$) (15). The retrospective cohort study carried out in 13 Ethiopian hospitals also found age and serum potassium level as factors associated with unfavorable treatment outcomes (20). Another study from Ethiopia also found HIV positivity, non-HIV comorbidities, clinical complications, extrapulmonary involvement, under nutrition, anemia, treatment delay, lower body weight, and older age as predictors of poor treatment outcome among MDR-TB patients (21). A study from India also revealed old age and illiteracy as conditions associated with a higher incidence of a poor treatment outcome (22).

A multicenter retrospective observational study conducted at three MDR-TB treatment centers in Southern Ethiopia to identify predictors of death revealed comorbidity, alcohol consumption, and history of poor adherence as risk factors that increase and hasten the risk of death. In this study,

HIV/AIDS, diabetes mellitus, and acute kidney injury were the frequent comorbidities. The existence of such comorbidities, primarily HIV/AIDS and diabetes mellitus were strongly related to immunosuppression (23).

A retrospective study carried out in China, among 2266 MDR-TB cases, also discovered HIV co-infection, old age, history of MDR-TB treatment, and low BMI as risk factors for poor treatment outcome (24). According to a cohort study in Indonesia, HIV co-infection, chronic kidney disease, and cavity lesions were found as significant risk factors for poor treatment outcomes of MDR-TB (25)

Even though St Peter Specialized Hospital is the largest MDR/RR-TB referral center in Ethiopia.with several hundreds of patients welcomed for MDR/RR –TB treatments,this facilitiy has a long history of MDR/RR-TB management.St Peter Hospital had about 1482 MDR/RR-TB patients managed at in patient and out patient levels .The treatment outcome of MD/RRR-TB at this center has not been studied. Therefore, the main aim of this study was to assess the treatment outcome of MDR/RR-TB and its determinant factors.

# 3. OBJECTIVE OF THE STUDY

## 3.1 GENERAL OBJECTIVE

- To assess treatment outcome of multidrug-resistant/rifampicine resistant (MDR/RR-TB) tuberculosis and its associated factors at St. Peter Specialized Hospital, Addis Ababa, Ethiopia from 2015 to 2020.

## 3.2 SPECIFIC OBJECTIVE

- To assess MDR/ RR -TB treatment outcomes at St. Peter Specialized Hospital, Addis Ababa, Ethiopia
- To identify factors associated with MDR/RR-TB treatment outcomes ,at St. Peter Specialized Hospital, Addis Ababa, Ethiopia.

# 4. METHODS

## 4.1 STUDY AREA

The study was conducted at St. Peter Specialized Hospital, Addis Ababa which provides MDR/RR-TB treatment. The Hospital was established in 1953.It is located in Gullele sub-city of Addis Ababa.It is administered under the Ethiopia Federal Ministry of Health.It is the first national hospital in the country to receive and care for MDR/RR-TB patients starting from April 2009. It was also recognized by the Ministry of Health as a center of excellence for MDR/RR -TB since 2012. This hospital is a referral hospital that receives patients from all parts of the country.But in the past few years, the Hospital grew from a single disease hospital into a multi-services health institution. The Hospital has already launched additional new services other than TB.

## 4.2 STUDY DESIGN AND PERIOD

A retrospective study was conducted among patients treated for drug-resistant tuberculosis from January 2015-December 2020.

## 4.3 STUDY POPULATION

### 4.3.1SOURCE POPULATION

All MDR/RR-TB patients who were treated at St. Peter Specialized Hospital.

### 4.3.2 STUDY POPULATION

All MDR/RR-TB patients who were treated at St. Peter Specialized Hospital between January 2015 and December 2020.

#### 4.3.2.1 INCLUSION CRITERIA

- All MDR/RR-TB patients treated at St. Peter Specialized Hospital during the study period

#### 4.3.2.2 EXCLUSION CRITERIA

- MDR/RR-TB patients who were still on therapy during the study period
- Patients with incomplete data

## 4.4 SAMPLE SIZE

The study included all MDR/RR -TB patients admitted to St. Peters' Specialized Hospital from January 2015 to December 2020.

## 4.5 STUDY VARIABLES

### 4.5.1 DEPENDENT VARIABLE

#### 4.5.1.1Successful treatement outcome

- Treatment Completed
- Cure

#### 4.5.1.2Poor treatement outcome

- Lost to follow-up (LTFU)
- Treatement failure
- Death

## 4.5.2 INDEPENDENT VARIABLES

### 4.5.2.1 Socio-Demographic variables

- Age at the beginning of treatment
- Sex
- Address
- Educational status
- Marital Status
- Occupation

### 4.5.2.2 Behavioral variables

- Use of alcohol
- Cigarette smoking
- Drug abuse

### 4.5.2.3 Clinical variables

- Prior TB treatment
- Presence of co-morbidity (diabetes, hypertension, liver disease, etc.)
- Presence of cavity lesion on Chest x-ray
- Site of infection
- Baseline BMI
- Baseline Sputum smear result
- Baseline Sputum culture result
- HIV Status
- Smear result conversion
- Culture result conversion
- Prior use of SLD
- Drug Susceptibility Test

## 4.6 OPERATIONAL DEFINITIONS

- **Cured -**from MDR/RR-TB those who completed treatment within 18 months to over 2 years, followed by at least two negative sputum cultures [24].
- **Completed treatment -**those patients who completed the anti TB regimen for at least 18 months [24].
- **Death**- apatient who died during treatment whatever the cause [24].
- **Failed treatment**- smear-positive patients who remained positive at the fifth month of treatment or smear-negative turning positive [24].
- **Lost to follow-up**- treated patients who did not come back to complete chemotherapy and there was no evidence of cure through the sputum result during the fifth month of therapy [24].
- **Successful treatment outcome-**patients meeting the definition of cure or treatment completed [24].
- **Poor treatment outcome-** refer to patients meeting the definition of death, lost to follow-up, and treatment failed [24].

## 4.7 DATA COLLECTION

### 4.7.1 Data collection tool

The questionnaire was prepared in English and used to collect the data from the MDR/RR-TB patient chart (Annex). It had three sections: sociodemographic data (such as sex, age, and residence), factors affecting treatment outcome, and the treatment outcomes of patients treated for MDR/RR-TB.

### 4.7.2 DATA collection:

MDR/RR-TB treatment register in St. Peter Specialized Hospital from January 2015-December 2020 was used as the data source. The data were collected by five data collectors and one supervisor who had experience in data collection. Data collectors were provided with training

about the aim and objective of the study by principal investigator. A detailed discussion of the contents of the questionnaire was also provided.

## 4.8 DATA QUALITY CONTROL

A structured questionnaire was used for data collection and its comprehensiveness and compatibility with the MDR/RR-TB register were evaluated. The overall completeness of the data was checked before entry to SPSS. During the data collection process, a double cleaning method was used by the investigator to ensure the quality of the data.

## 4.9 DATA ANALYSIS

Data were coded and entered into Excel. After completion of data entry, data were re-checked for completeness and any coding errors before analysis. After exporting the data from Excel to SPSS, both descriptive and inferential statistics were carried out to meet the objectives.

During descriptive statistical analysis, categorical variables were described using counts, percentages, and 95% confidence interval for percentages. Continuous variables like age were also described using an appropriate combination of measure of central tendency and measure of dispersion.

Inferential statistics (i.e. binary logistic regression) was conducted to identify factors associated with overall treatment outcome status. Variables with $p<0.25$ during univariable analysis were selected for fitting multivariable logistic regression analysis. Odds ratio, 95% confidence interval, and p-value results are reported to display the magnitude, direction, precision, and significance of association (both crude and adjusted) between the independent variables and MDR/RR-TB treatment outcome status. Statistical significance was declared for statistical results with $p<0.05$. The goodness of fit and multicollinearity was checked using the Hosmer-Lemeshow test and Variance Inflation Factor (VIF), respectively. Overall results are presented in the form of text, table, and graph.

## 4.10 ETHICAL CONSIDERATION=

Ethical clearance was obtained from the scientific and ethics review committee of CDT-Africa, College of Health Sciences. Letter was wriiten for permission to access data from the concerned offices at St. Peter Specialized Hospital. Confidentiality of the information collected was maintained. Patient identification numbers like medical record numbers were removed and replaced with codes. Data will not be shared to an unauthorized third party.

### 4.11 DISSEMINATION OF THE RESULT

The finding of the study will be presented to CDT Africa Addis Ababa University, College of Health Science, and St. Peter Specialized Hospital. It will also be presented and disseminated to all stakeholders; public and concerned bodies through a presentation in different professional meetings. A manuscript will be sent to an international or national peer-reviewed journal for publication.

## 5. Result

In this study,out of the total number of patients treated during the study period we reviewed 335 records because data was unavailable due to incomplete record or lost chart.

### 5.1 Sociodemographic and behavioral characteristics

The mean age (SD) of the participants was 30 (12) years. Nearly three-fourths 244/335 (72.8%) of the patients were from Addis Ababa and more than half 170/335 (50.7%) of them were males. Regarding marital status, two-thirds 220/335 (65.7%) and one-fifth 72/335 (21.5%) of the participants were single and married, respectively. More than half of the participants were followers of the orthodox religion. Concerning family size, three-fourth of the participants lived in a family composed of four or fewer members. Smokers, alcohol users, and drug abusers accounted for 7.2%, 12.8%, and 4.5% of the participants, respectively. (***Table 1***).

***Table 1****: Sociodemographic and behavioral characteristics of the participants, St. PeterSpecialized Hospital, 2015-2020.*

| Variables | | | 95% CI of percent | |
|---|---|---|---|---|
| Categories | Frequency (N=335) | Percent | Lower limit | Upper limit |

| | | | | |
|---|---|---|---|---|
| Region | | | | |
| Addis Ababa | 244 | 72.8 | 67.9 | 77.4 |
| Amhara | 9 | 2.7 | 1.3 | 4.8 |
| Oromia | 53 | 15.8 | 12.2 | 20.0 |
| SNNP | 12 | 3.6 | 2.0 | 6.0 |
| Other | 17 | 5.1 | 3.1 | 7.8 |
| Gender | | | | |
| Female | 165 | 49.3 | 43.9 | 54.6 |
| Male | 170 | 50.7 | 45.4 | 56.1 |
| Marital status | | | | |
| Divorced | 16 | 4.8 | 2.9 | 7.5 |
| Married | 72 | 21.5 | 17.4 | 26.1 |
| Under age | 12 | 3.6 | 2.0 | 6.0 |
| Separated | 3 | 0.9 | 0.3 | 2.4 |
| Single | 220 | 65.7 | 60.5 | 70.6 |
| Widowed | 12 | 3.6 | 2.0 | 6.0 |
| Family size | | | | |
| <5 | 256 | 76.4 | 71.7 | 80.7 |
| 5+ | 79 | 23.6 | 19.3 | 28.3 |

**Table 1** continued…

| Variables | | | 95% CI of percent | |
|---|---|---|---|---|
| Categories | Frequency (N=335) | Percent | Lower limit | Upper limit |
| `Education status | | | | |
| Illiterate | 84 | 25.1 | 20.7 | 29.9 |
| Primary | 100 | 29.9 | 25.1 | 34.9 |
| Secondary | 95 | 28.4 | 23.7 | 33.4 |
| Higher | 51 | 15.2 | 11.7 | 19.4 |
| Not applicable | 5 | 1.5 | 0.6 | 3.2 |
| Occupation | | | | |
| Daily laborer | 43 | 12.8 | 9.6 | 16.7 |
| Farmer | 12 | 3.6 | 2.0 | 6.0 |
| Government employee | 37 | 11.0 | 8.0 | 14.7 |
| Housemaid | 12 | 3.6 | 2.0 | 6.0 |
| Merchant | 4 | 1.2 | 0.4 | 2.8 |
| Not applicable | 9 | 2.7 | 1.3 | 4.8 |
| Private employee | 92 | 27.5 | 22.9 | 32.4 |
| Student | 40 | 11.9 | 8.8 | 15.7 |
| Unemployed | 86 | 25.7 | 21.1 | 30.1 |
| Religion | | | | |
| Muslim | 46 | 13.7 | 10.4 | 17.7 |

| | | | | |
|---|---|---|---|---|
| Orthodox | 182 | 54.3 | 49.0 | 59.6 |
| Other | 52 | 15.5 | 11.9 | 19.7 |
| Protestant | 55 | 16.4 | 12.7 | 20.7 |
| Smoker | | | | |
| Yes | 24 | 7.2 | 4.8 | 10.3 |
| No | 311 | 92.8 | 89.7 | 95.2 |
| Alcohol | | | | |
| Yes | 43 | 12.8 | 9.6 | 16.7 |
| No | 292 | 87.2 | 83.3 | 90.4 |
| Drug abuse | | | | |
| Yes | 15 | 4.5 | 2.6 | 7.1 |
| No | 320 | 95.5 | 92.9 | 97.4 |
| Body Mass Index (BMI) | | | | |
| Normal/Overweight | 70 | 20.0 | 16.8 | 25.5 |
| Underweight | 265 | 79.1 | 74.5 | 83.2 |

N.B. Not applicable represents children and infants who are not candidates for formal education and job due to young age.

## 5.2 Clinical characteristics

More than half 188/335 (56.1%) of patients were previously treated for tuberculosis at least once. Comorbidity, cavitary lesion, HIV were reported in 150/335 (44.8%), 137/335 (40.9%), and 94/335 (28.1%) of patients, respectively. Only 27/335 (8.1%) of patients had a history of second-line drug (SLD) use or were previously treated for MDR/RR-TB (

**Table *2***).

***Table 2:*** *Clinical characteristics of the MDR-TB patients, St. Peter Specialized Hospital, 2015-2020.*

| Variables | | | 95% CI of percent | |
|---|---|---|---|---|
| Categories | Frequency (N=335) | Percent | Lower limit | Upper limit |
| Number of previous TB treatments | | | | |
| 0 | 60 | 17.9 | 14.1 | 22.3 |
| 1 | 188 | 56.1 | 50.8 | 61.4 |
| 2 | 69 | 20.6 | 16.5 | 25.2 |
| 3 & above | 18 | 5.4 | 3.4 | 8.4 |
| Contact history | | | | |
| Yes | 42 | 12.5 | 9.3 | 16.4 |
| No | 293 | 87.5 | 83.6 | 90.7 |

| | | | | |
|---|---|---|---|---|
| Comorbidity | | | | |
| Yes | 150 | 44.8 | 39.5 | 50.1 |
| No | 185 | 55.2 | 49.9 | 60.5 |
| Cavity lesion | | | | |
| Y es | 137 | 40.9 | 35.7 | 46.2 |
| No | 198 | 59.1 | 53.8 | 64.3 |
| Group | | | | |
| After failure of first treatment | 74 | 22.1 | 17.9 | 26.8 |
| After failure of retreatment | 3 | 0.9 | 0.3 | 2.4 |
| Lost to follow-up | 3 | 0.9 | 0.3 | 2.4 |
| New | 164 | 49.0 | 43.6 | 54.3 |
| Relapse | 91 | 27.2 | 22.6 | 32.1 |
| HIV | | | | |
| Negative | 241 | 71.9 | 67.0 | 76.5 |
| Positive | 94 | 28.1 | 23.5 | 33.0 |
| Prior second-line drug use | | | | |
| No | 308 | 91.9 | 88.7 | 94.5 |
| Yes | 27 | 8.1 | 5.5 | 11.3 |

## 5.3 Diagnosis and outcome-related characteristics of patients

More than 90% of MDR/RR-TB cases were detected byGene-Xpert. Sputum and culture were positive in 58.2% and 54.3% of patients, respectively. Almost all 327/335 (97.6%) MDR/RR - TB cases were resistant to rifampicin only. Treatment completion and cure were observed in 41.2% and 30.1% of patients, respectively. Death, loss to follow-up, and failure of treatment occurred in 42/335 (12.5%0, 47/335 (14.0%), and 7/335 (2.1%), respectively. Overall, treatment success was achieved in 71.3% of the patients (

**The** majority of the patients(308, 91.9%) were diagnosed by Gene-Xpert,327 (97.6%) of patients were resistant to Rifampicin, 8 (2.4%) were resistant to both Rifampicin and Isoniazid, 138(41.2%) of patients have completed their treatment followed by 101(30.2%) and only 7(2.1%) had a failure of treatment

***Table 3***). But this treatment success was significantly different by HIV status ($\chi^2(1) = 16.410$, $p<0.001$). As shown in figure 1, treatment success was higher by 23% among patients who were HIV negative compared to those who were HIV positive (**Figure 1**).

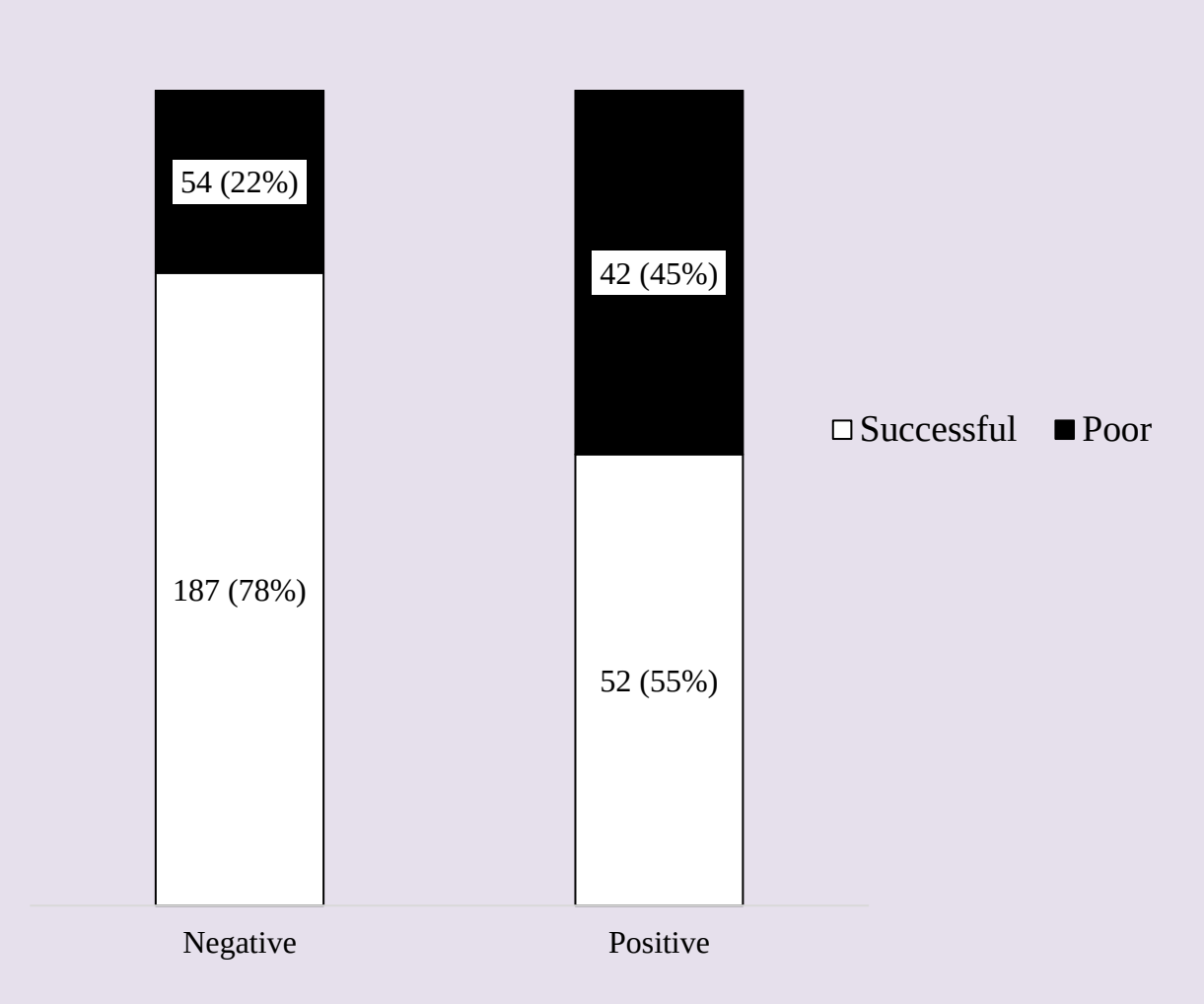


**Figure 1:***Demonstration of the percentage of overall treatment success by HIV status of the patients, N=335.*

The majority of the patients(308, 91.9%) were diagnosed by Gene-Xpert,327 (97.6%) of patients were resistant to Rifampicin, 8 (2.4%) were resistant to both Rifampicin and Isoniazid, 138(41.2%) of patients have completed their treatment followed by 101(30.2%) and only 7(2.1%) had a failure of treatment

***Table 3**: Diagnosis and treatment outcome-related characteristics, St. Peter SpecializedHospital, 2015-2020.*

| Variables | Frequency | | 95% CI of percent | |
|---|---|---|---|---|
| Categories | (N=335) | Percent | Lower limit | Upper limit |
| Method of diagnosis | | | | |
| Drug susceptibility test (DST) | 2 | 0.6 | 0.1 | 1.9 |
| Gene expert | 308 | 91.9 | 88.7 | 94.5 |
| Line probe assay (LPA) | 25 | 7.5 | 4.8 | 11.5 |
| Smear | | | | |
| Negative | 91 | 27.2 | 22.6 | 32.1 |
| Positive | 195 | 58.2 | 52.9 | 63.4 |
| Unavailable | 49 | 14.6 | 11.2 | 18.7 |
| Culture | | | | |
| Contaminated | 4 | 1.2 | 0.4 | 2.8 |
| Negative | 36 | 10.7 | 7.8 | 14.4 |
| Positive | 182 | 54.3 | 49.0 | 59.6 |
| Unavailable | 113 | 33.7 | 28.8 | 38.9 |
| Sputum conversion | | | | |
| Negative | 224 | 66.9 | 61.7 | 71.7 |
| Positive | 15 | 4.5 | 2.6 | 7.1 |
| Unavailable | 96 | 28.7 | 24.0 | 33.7 |
| Culture conversion | | | | |
| Negative | 235 | 70.1 | 65.1 | 74.9 |
| Positive | 25 | 7.5 | 5.0 | 10.6 |
| Unavailable | 75 | 22.4 | 18.2 | 27.1 |
| Type of resistance | | | | |
| Isoniazid and Rifampicin resistant | 8 | 2.4 | 1.1 | 4.5 |
| Rifampicin resistant | 327 | 97.6 | 95.5 | 98.9 |
| Condition after last follow-up | | | | |
| Completed | 138 | 41.2 | 36.0 | 46.5 |
| Cured | 101 | 30.2 | 25.4 | 35.2 |
| Died | 42 | 12.5 | 9.3 | 16.4 |
| Failed | 7 | 2.1 | 0.9 | 4.1 |
| Lost to follow-up | 47 | 14.0 | 10.6 | 18.1 |
| Overall outcome | | | | |
| Poor | 96 | 28.7 | 24.0 | 33.7 |
| Successful | 239 | 71.3 | 66.3 | 76.0 |

## 5.4 Predictors of poor treatment outcome

To identify factors associated with the overall outcome of patients treated for MDR/RR-TB, logistic regression was fitted. During univariable analysis, four variables (i.e., gender, alcohol use, cavity lesion, and HIV status) were significantly associated with the overall outcome. However, during multivariable analysis, only alcohol use and HIV status were significantly related to the overall outcome. Accordingly, the adjusted odds of poor treatment outcome were twice higher in those who had a habit of alcohol drinking. Likewise, the adjusted odds of poor treatment outcome were more than 2-folds higher in patients who were positive for HIV (**Table 4**).

**Table 4***: Predictors of overall treatment outcome in patients treated for MDR/RR-TB, St. Peter Specialized Hospital , 2015-2020.*

| ***Independent variables*** | ***COR (95% CI)*** | ***p value*** | ***AOR (95% CI)*** | ***p value*** |
|---|---|---|---|---|
| Age | 1.02 (0.99, 1.03) | 0.076 | 1.01 (0.99, 1.03) | 0.516 |
| Gender | | | | |
| Male | 1.63 (1.01, 2.63) | 0.046 | 1.40 (0.84, 2.35) | 0.195 |
| Female | 1 | | 1 | |
| BMI | | | | |
| Underweight | 1.46 (0.79, 2.70) | 0.229 | 1.56 (0.82, 3.00) | 0.177 |
| Normal/Overweight | 1 | | 1 | |
| Alcohol | | | | |
| Yes | 2.47 (1.29, 4.75) | 0.007 | 2.07 (1.04, 4.15) | 0.039 |
| No | 1 | | 1 | |
| Cavity lesion | | | | |
| Yes | 1.79 (1.11, 2.89) | 0.017 | 1.44 (0.86, 2.40) | 0.162 |
| No | 1 | | 1 | |
| HIV test result | | | | |
| Positive | 2.80 (1.68, 4.64) | <0.001 | 2.43 (1.42, 4.15) | 0.001 |
| Negative | 1 | | 1 | |

The final model was good fit for the data, $\chi^2(8) = 2.99$, $p = 0.935$. There was no multicollinearity issue in the final model (maximum VIF=1.13).
**AOR**= Adjusted Odds Ratio, **CI**= Confidence Interval, **COR**= Crude Odds Ratio

## 5.5 Predictors of death among MDR/RR-TB patients

A multivariable logistic regression composed of five variables was conducted to find predictors significantly associated with death among MDR/RR-TB patients. During univariable analysis, four variables (i.e., age, prior SLD use, cavity lesion, and HIV status) were significantly associated with death. However, during multivariable analysis, only age and HIV status were significantly related to death. Accordingly, the adjusted odds of death was found to increase by 5% as age advances by one year. Similarly, the adjusted odds of death was about 4-folds higher in patients who were positive for HIV (**Table 5**).

**Table 5:** *Predictors of death among patients treated for MDR-TB, St. Peter Specialized Hospital , 2015-2020.*

| ***Independent variables*** | ***COR (95% CI)*** | ***p value*** | ***AOR (95% CI)*** | ***p value*** |
|---|---|---|---|---|
| Age | 1.06 (1.03, 1.09) | <0.001 | 1.05 (1.02, 1.08) | <0.001 |
| Prior SLD use | | | | |
| Yes | 2.73 (1.08, 6.92) | 0.034 | 1.96 (0.70, 5.60) | 0.194 |
| No | 1 | | 1 | |
| Alcohol | | | | |
| Yes | 1.73 (0.74, 4.05) | 0.203 | 1.36 (0.52, 3.51) | 0.531 |
| No | 1 | | 1 | |
| Cavity lesion | | | | |
| Yes | 2.66 (1.37, 5.19) | 0.004 | 1.79 (0.86, 3.66) | 0.118 |
| No | 1 | | 1 | |
| HIV test result | | | | |
| Positive | 5.38 (2.73, 10.61) | <0.001 | 3.81 (1.86, 7.79) | <0.001 |
| Negative | 1 | | 1 | |

The final model was good fit for the data, $\chi^2(8) = 5.6$, $p = 0.692$. There was no multicollinearity issue in the final model (maximum VIF=1.10).

**AOR**= Adjusted Odds Ratio, **CI**= Confidence Interval, **COR**= Crude Odds Ratio, **SLD**= Second-Line Drug

# 6. Discussion

In this study, 41.2% of MDR/RR-TB patients completed their treatment, and 30.1% were cured. The overall treatment success was 71.3% (95% CI: 66.3 -76.0%). Comparable results were also reported from studies carried out in the Oromia and Amhara regions of Ethiopia, Tanzania, Vietnam, and Taiwan (24, 26–29). Lower treatment success rates were reported from Indonesia (50%), India (56.3%), and Brazil (60%) (22,25,30).Death, loss to follow-up, and failure of treatment also occurred in 12.5%, 13.7%, and 2.1% of the patients , respectively.

higher among MDR/RR-TB patients who are either elderly and/or co-infected with HIV. Factors significantly associated with overall MDR/RR-TB treatment outcome were alcohol consumption and HIV status. Thus, the adjusted odds of poor treatment outcome was remarkably higher in MDR/RR-TB patients who consumed alcohol habitually and were positive for HIV. Concerning mortality among MDR/RR-TB patients, the odds of death was significantly

Regarding factors associated with poor treatment outcome, HIV was found to increase the odds of poor treatment outcome more than 2-fold. In line with this finding, the study in the Oromia region also found a higher risk of poor treatment outcomes in individuals with HIV (26). Likewise, a systematic review and meta-analysis on poor treatment outcome and its predictors among drug-resistant tuberculosis patients in Ethiopia also revealed a nearly 2-fold risk of poor treatment outcome in MDR/RR-TB patients co-infected with HIV (21). Similarly, studies from Brazil and Vietnam also revealed a 3-fold risk of poor treatment outcome in MDR-TB patients co-infected with HIV (24,30).

Tuberculosis is said to facilitate HIV replication and viral mutation rates through proinflammatory cytokine production.Cytokines upsurge HIV viral replication and diversity, hence facilitating immunosuppression (31). Owing to the weak cellular immunity of HIV-positive individuals, MDR/RR-TB patients cannot cope with co-infection (21). MDR/RR-TB patients with HIV also suffer a lot from drug-drug interactions following the consumption of many drugs. As a result, they are prone to medication non-adherence and side effects (32). Microbiological confirmation is also problematic to get in HIV positive patients, which leads to delayed treatment of MDR/RR-TB patients (33). Subsequently, MDR/RR-TB patients who are co-infected with HIV are pre-disposed to treatment failure due to the impaired cellular immunity, drug-drug interactions, poor drug adherence, and delayed diagnosis of MDR/RR-TB.

The mortality rate among participants of this study who were co-infected with HIV was 27.7% and significantly higher than those who were negative for HIV (6.6%). The adjusted odds of death was 4 times higher among MDR/RR-TB patients co-infected with HIV. In tune with this observation, a meta-analysis study conducted among 11,920 MDR/RR-TB patients also found a higher odds of death in individuals co-infected with HIV (AOR=2·4; 95% CI 2·0–2·9) (34). Excess death in this group of individuals is due to rapid progression of tuberculosis, mycobacteriosis, and HIV-related opportunistic infections (35,36).

The other important predictor of death was age. The odds of death was found to increase by 5% as age increases by one-year. A study conducted among 451 MDR-TB patients of three hospitals in Amhara, Ethiopia found a  risk of death that increased by 4% for each one year increase in age (37). Supporting this findings, a study carried out in Taiwan also found more than 6-fold increased risk of death in MDR-TB patients who are older than 65 years (38). Elderly people are prone to death due to presence of multiple comorbidities or chronic diseases, physical deterioration, and weakened immunity (39).

Another predictor of poor treatment outcome, in our study, was alcohol consumption. Accordingly, the odds of poor treatment outcomes were double in those MDR/RR-TB patients who consumed alcohol.A systematic review and meta-analysis study also found twice the risk of poor treatment outcome in MDR/RR-TB patients who consumed alcohol (40). Likewise, a study in Russia also found more than a 3-fold increased risk of poor treatment outcome in such group of patients(41).In tune with these findings, a multi-center study of Southern Ethiopia found about four times higher hazard of poor survival in MDR/RR-TB patients who consumed alcohol (23). People who consumealcohol are more likely to have poor adherence to medications, loss to follow-up, and death (40,41). As a result, they are more prone to poor treatment outcomes. Alcohol also intensifies adverse drug reactions including liver toxicity. Besides, Alcohol consumption also diminishes general health and may weaken immune responses against Mycobacterium tuberculosis (42). Worldwide, around 10% of TB-related deaths are attributable to alcohol use (43).

# 7. Conclusion

This study was not free of limitations. First, The retrospective nature of the data source restricted us from analyzing data of all patients who were MDR/RR-TB patients during the study period.

The reason for this limitation was incomplete data, improper handling of patient records, and some records were unavailable. This may negatively affect the power and generalizability of the study. Second, important variables like drug adherence were not assessed due to the secondary nature of the data. Third, frequency and amount were not evaluated for alcohol use and smoking. Last, but not least, it was difficult to extract information related to co morbidities.

The study has provided some evidence that treatment success rates have increased over time.The overall treatment success was consistent with findings from other studies carried out in different regions of Ethiopia.

A higher risk of poor treatment outcome was observed among patients who consumed alcohol or were co-infected with HIV/AIDS. Elderly patients and/or co-infected with HIV were also more prone to death.

# 8. Recommendation

MDR/RR-TB treatment is a challenge owing to the chronic nature of the disease, long duration of treatment, and numerous drugs used in the regimen. To maximize drug adherence and handle adverse events, alcohol users, patients with comorbidity like HIV/AIDS, and the elderly should be given great emphasis during therapy. Furthermore, a deeper knowledge of factors affecting treatment outcomes of MDR/RR-TB patients is mandatory to make improvements in the success rate of MDR/RR-TB treatment and proper treatment of drug susceptible TB and early detection and treatment of MDR/RR-TB before complication developed along with preventing contacts with MDR/RR-TB not to spread the disase is also very important.

Therefore,FederalMinisties of Health should establish strategies to avert factors associated with poor treatementoutcomes.Inaddition,researchers should conduct others researchers on variables not included in this study and prospective design givig policy makers level recommendation.

# 9. References


1. Talip BA, Sleator RD, Lowery CJ, Dooley JSG, Snelling WJ. An Update on Global Tuberculosis (TB). Infect Dis Res Treat. 2013;6:IDRT.S11263.

2. Lange C, Abubakar I, Alffenaar JWC, Bothamley G, Caminero JA, Carvalho ACC, et al. Be Po. Eur Respir J. 2014;44(1):23–63.

3. Rodger AJ, Story A, Fox Z, Hayward A. HIV prevalence and testing practices among tuberculosis cases in London: a missed opportunity for HIV diagnosis? Thorax. 2010 Jan;65(1):63–9.

4. Meya DB, McAdam KPWJ. The TB pandemic: an old problem seeking new solutions. J Intern Med. 2007 Apr;261(4):309–29.

5. Amare H, Gelaw A, Anagaw B, Gelaw B. Smear positive pulmonary tuberculosis among diabetic patients at the Dessie referral hospital, Northeast Ethiopia. Infect Dis poverty. 2013 Mar;2(1):6.

6. Corbett EL, Charalambous S, Moloi VM, Fielding K, Grant AD, Dye C, et al. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. Am J Respir Crit Care Med. 2004 Sep;170(6):673–9.

7. Eshetu F, Ahmed J, Eskinder B, Feleke B, Haile A, Hanson J. in Collaboration With Center for Disease Prevention and Control (Cdc). 2014;(December).

8. Angelo RRS. As Ethiopia Moves toward Tuberculosis Elimination, Success Requires Higher Investment. البيئة للدراسات اسيوط مجلة. 2001;الحا العدد(March 2016):43.

9. Fekadu S, Teshome W, Alemu G. Prevalence and determinants of Tuberculosis among HIV infected patients in south Ethiopia. J Infect Dev Ctries. 2015 Aug;9(8):898–904.

10. Eshetie S, Alebel A, Wagnew F, Geremew D, Fasil A, Sack U. Current treatment of multidrug resistant tuberculosis in Ethiopia: an aggregated and individual patients' data analysis for outcome and effectiveness of the current regimens. BMC Infect Dis. 2018 Sep;18(1):486.

11. FDRE M. GUIDELINES FOR MANAGEMENT OF TB, DR-TB AND LEPROSY IN ETHIOPIA. 6th ed. Addis Ababa; 2017. 61–62 p.

12. Riello FN, Brígido RTS, Araújo S, Moreira TA, Goulart LR, Goulart IMB. Diagnosis of mycobacterial infections based on acid-fast bacilli test and bacterial growth time and implications on treatment and disease outcome. BMC Infect Dis. 2016 Apr;16:142.

13. Phuong NTM, Nhung N V., Hoa NB, Thuy HT, Takarinda KC, Tayler-Smith K, et al. Management and treatment outcomes of patients enrolled in MDR-TB treatment in Viet Nam. Public Heal Action. 2016;6(1):25–31.

14. Zhang L, Meng Q, Chen S, Zhang M, Chen B, Wu B, et al. Treatment outcomes of multidrug-resistant tuberculosis patients in Zhejiang, China, 2009-2013. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2018 Apr;24(4):381–8.

15. Gele AA, Bjune G, Abebe F. Pastoralism and delay in diagnosis of TB in Ethiopia. BMC Public Health. 2009 Jan;9:5.

16. Merid MW, Gezie LD, Kassa GM, Muluneh AG, Akalu TY, Yenit MK. Incidence and predictors of major adverse drug events among drug-resistant tuberculosis patients on second-line anti-tuberculosis treatment in Amhara regional state public hospitals; Ethiopia: a retrospective cohort study. BMC Infect Dis. 2019 Mar;19(1):286.

17. Marais E, Mlambo CK, Lewis JJ, Rastogi N, Zozio T, Grobusch MP, et al. Treatment outcomes of multidrug-resistant tuberculosis patients in Gauteng, South Africa. Infection. 2014;42(2):405–13.

18. Abdella K, Abdissa K, Kebede W, Abebe G. Drug resistance patterns of Mycobacterium tuberculosis complex and associated factors among retreatment cases around Jimma, Southwest Ethiopia. BMC Public Health. 2015 Jul;15:599.

19. Girum T, Muktar E, Lentiro K, Wondiye H, Shewangizaw M. Epidemiology of multidrug-resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of the prevalence, determinants and treatment outcome. Trop Dis Travel Med vaccines. 2018;4:5.

20. Molie T, Teklemariam Z, Klinkenberg E, Dessie Y, Kumsa A, Mohammed H, et al. Intensive phase treatment outcome and associated factors among patients treated for multi drug resistant tuberculosis in Ethiopia: A retrospective cohort study. BMC Infect Dis. 2019;19(1):1–10.

21. Alemu A, Bitew ZW, Worku T. International Journal of Infectious Diseases Poor treatment outcome and its predictors among drug-resistant tuberculosis patients in Ethiopia : A systematic review and. Int J Infect Dis [Internet]. 2020;98:420–39. Available from: https://doi.org/10.1016/j.ijid.2020.05.087

22. Nagpal M, Chawla S, Devgun P, Chawla N. Socio-demographic determinants of treatment outcome in multidrug resistant tuberculosis cases registered under Programmatic management of drug resistant tuberculosis services in Amritsar. Punjab. 2019;6(6):2688–93.

23. Bade AB, Ayele T, Id M. Survival status and its predictors among multi-drug resistance tuberculosis treated patients in Ethiopia : Multicenter observational study.PLoS ONE 15(11):e0241684.2020;108:111.Availablefrom:http://dx.doi.org/10.1371/journal.pone.0241684

24. Van LH, Phu PT, Vinh DN, Son VT, Hanh NT, Thanh L, et al. Risk factors for poor treatment outcomes of 2266 multidrug-resistant tuberculosis cases in Ho Chi Minh City : a retrospective study.*BMC Infect Dis***20,** 164 . https://doi.org/10.1186/s12879-020-4887-1 2020;1–10.

25. Yuwono A, Id S, Id CP, Santoso P, Lestari BW. Factors affecting outcome of longer regimen multidrug-resistant tuberculosis treatment in West Java Indonesia : A retrospective cohort study. PLoS ONE 16(2): e0246284. 2021;1–13. Available from: http://dx.doi.org/10.1371/journal.pone.0246284

26. Id DW, Assefa T, Aman R, Tekalegn Y. Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region,Ethiopia. PLoS ONE 14(10): e0224025. https://doi.org/10.1371/journal.pone.0224025. 2019;415:1–14.

27. Alene KA, Viney K, McBryde ES, Tsegaye AT, Clements ACA. Treatment outcome in patients with multidrug-resistant tuberculosis in North-West Ethiopia. Trop Med Int Heal. 22(3):351–62.

28. Leveri TH, Lekule I, Mollel E, Lyamuya F, Kilonzo K. Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania.*Tuberculosis Research and*

*Treatment*, vol. 2019, Article ID3569018, 10pages, 2019. https://doi.org/10.1155/2019/3569018.

29. Lin C-B, Sun H-C, Chiang C-Y, Wu C-W, Chou H-W, Tang T-Q, et al. Treatment outcomes for multidrug-resistant tuberculosis in Eastern Taiwan. Tzu Chi Med J. 2019;31(1):35–9.

30. Bastos ML, Cosme LB, Fregona G, Nascimento T, Bertolde AI, Zandonade E, et al. Treatment outcomes of MDR-tuberculosis patients in Brazil : a retrospective cohort analysis. *BMC Infect Dis***17,** 718 (2017). https://doi.org/10.1186/s12879-017-2810-12017;1–12.

31. Wang J, Shen H. Review of cigarette smoking and tuberculosis in China: intervention is needed for smoking cessation among tuberculosis patients. BMC Pub Heal. 2009; 9 (292):1–9. https://doi.org/10. 1186/1471-2458-9-292 PMID: 19674472.

32. Azeez A, Ndege J, Mutambayi R. Associated factors with unsuccessful tuberculosis treatment outcomes among tuberculosis/HIV coinfected patients with drug-resistant tuberculosis.Int J Mycobacteriol . 2018; 7(4):347. https://doi.org/10.

33. Magis-Escurra C, Gu¨nther G, Lange C, Alexandru S, Altet N, Avsar K, et al. Treatment outcomes of MDR-TB and HIV co-infection in Europe. Eur Respir J. 2017; 49(6). https://doi.org/10.1183/13993003. 02363-2016 PMID: 28596434.

34. Bisson GP, Bastos M, Campbell JR, Bang D, Brust JC, Isaakadis P, et al. Mortality in adults with multidrug-resistant tuberculosis and HIV by antiretroviral therapy and tuberculosis drug use: an individual patient data meta-analysis. Lancet [Internet]. 2020;396(10248):402–11.Availablefrom:http://dx.doi.org/10.1016/S0140-6736(20)31316-7

35. Wong EB, Omar T, Setlhako GJ, et al. Causes of death on antiretroviral therapy: a post-mortem study from South Africa. PLoS ONE 2012; 7: e47542.

36. van der Walt M, Lancaster J, Shean K. Tuberculosis case fatality and other causes of death among multidrug-resistant tuberculosis patients in a high HIV prevalence setting, 2000–2008, South Africa. PLoS ONE 2016; 11: e0144249.

37. Kassa GM, Tadesse A, Gelaw YA, Alemayehu TT, Tsegaye AT, Tamirat KS, et al.

Predictors of mortality among multidrug- resistant tuberculosis patients in central Ethiopia : a retrospective follow-up study. 2020; Epidemiol Infect. 2020 Oct 15;148:e258. doi:10.1017/S0950268820002514.PMID:33054897;PMCID: PMC7689597.

38. Yu M, Chiang C, Lee J, Chien S, Lin C, Lee S, et al. Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan : Tackling Loss to Follow-up.Clin Infect Dis. 2018 Jul 2;67(2):202-210. doi: 10.1093/cid/ciy066. PMID: 29394358; PMCID: PMC6030934.

39. Abubakar M, Ahmad N, Ghafoor A, Latif A, Ahmad I, Atif M, et al. Treatment Outcomes of Extensively Drug-Resistant Tuberculosis in Pakistan : A Countrywide Retrospective Record Review. Front. Pharmacol.,2021;12(March):1–9.

40. Ragan EJ, Kleinman MB, Sweigart B, Gnatienko N, Parry CD, Horsburgh CR, et al. The impact of alcohol use on tuberculosis treatment outcomes: A systematic review and meta-analysis. Int J Tuberc Lung Dis. 2020;24(1):73–82.

41. Miller AC, Gelmanova IY, Keshavjee S, Atwood S, Yanova G, Mishustin S, et al. Alcohol use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation. Int J Tuberc Lung Dis. 2012;16(7):891–6.

42. Myers B, Bouton TC, Ragan EJ, White LF, Mcilleron H, Theron D, et al. Impact of alcohol consumption on tuberculosis treatment outcomes: a prospective longitudinal cohort study protocol. BMC Infect Dis. 2018;1–9. https://doi.org/10.1186/s12879-017-2892-9 P.

43. Bronwyn M, Tara C, Elizabeth J, Laura F, Helen M, Charles D et.al. Impact of alcohol consumption on tuberculosis treatment outcomes: a prospective longitudinal cohort study protocol. BMC Infect Diseases. 2018; 18:488.

# 10.Annex

## 1. The Questionnaire

**PART 1: Socio-demographic and socioeconomic characteristics**

| S. No | Questions | Patient Categories |
|---|---|---|
| 1 | Age | ---------- |
| 2 | Sex | Male |
| | | Female |
| 3 | Marital Status | Married |
| | | Divorced |
| | | Widowed |
| | | Single |

| | | |
|---|---|---|
| 4 | Educational Status | Illiterate |
| | | 1-8 |
| | | 9-12 |
| | | diploma |
| | | University degree & above |
| 5 | Occupation | Farming |
| | | Government employee |
| | | Business |
| | | Daily laborer |
| | | Unemployed |
| | | Other<br>Specify |
| 6 | Monthly income | ---------- |
| 7 | Religion | 1.Orthodox Christian |
| | | 2.Musilim |
| | | 3.Protestant |
| | | 4.Others |
| 8 | Family number(size) | ---------- |
| **9** | Address (region) of patients | 1. Tigray<br>2. Afare<br>3. Amhara<br>4. Oromia<br>5. Somali<br>6. BenshanguleGumez |

| | | |
|---|---|---|
| | | 7. SNNPR G<br>8. Gambela<br>9. Hararie<br>10. Addis Ababa<br>11. Dire Dawa<br>12. Unrecorded |

**Part 2: Behavioral factors Variables**

| S,n.o | Variable | Response |
|---|---|---|
| 1 | Cigarette smoking | 1. Yes<br>2. No<br>3. Unrecorded |
| 2 | If your answer is yes | 1. Current smoker<br>2. X-smoker<br>3. Average daily smoker<br>4. All pocket smoker |
| 3 | Alcohol intake | 1. Yes<br>2. No<br>3. Unrecorded |
| 4 | If your answer is yes | 1. Occasionally<br>2. Always<br>3. Often |
| 5 | History of drug abuse | 1. Yes<br>2. No |
| 5.1 | If yes to question 5 how frequent | 1. occasionally |
| | | 2.often |
| | | 3.daily |

**Part 3 : Clinical Variables**

| No | Variables | |
|---|---|---|
| **1.** | Current TB status | New |
| | | Previouslytreated |
| **2.** | History of contact with MDR-TB patients/contact history | Yes |
| | | No |
| **3.** | HIV/AIDS Sero-status | Positive |
| | | Negative |
| **4.** | Site of infection | Extra-pulmonary |
| | | Pulmonary |
| **5.** | Chronic illness | Yes |
| | | No |
| 5.1 | If Yes please specify | …….. |
| 6 | Cavity Lesion on CXR | Yes |
| | | No |
| 7 | Had baseline BMI | ……..m/kg |
| 8 | Baseline Sputum smear Result | Positive |
| | | Negative |

| | | |
|---|---|---|
| 9 | Baseline Sputum culture Result | Yes |
| | | No |
| 9.1 | If Yes Please Specify Result | …….. |
| 10 | Sputum conversion test | Yes |
| | | No |
| 11 | Culture conversion test | Yes |
| | | No |
| 12 | Prior Use of SLD | Yes |
| | | No |
| 13 | Drug Susceptibility test | Yes |
| | | No |
| 13.1 | If Yes, Please specify result | …….. |
| 14 | Treatment out come | 1. Cured<br>2.Treatment completed<br>3.Died<br>4.Failure<br>5.Lost to follow up |