



**ST. PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE
DEPARTMENT OF PUBLIC HEALTH**

**MULTIDRUG RESISTANT TUBERCULOSIS TREATMENT NON- ADHERENCE
AND ASSOCIATED FACTORS AMONG PATIENTS ATTENDING PUBLIC
HOSPITALS IN SOUTHERN NATION NATIONALITIES AND PEOPLES
REGION, ETHIOPIA**

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**SEPTEMBER, 2019
ADDIS ABABA, ETHIOPIA**



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APPROVAL SHEET

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ABBREVIATION AND ACRONYMS

AEs	Adverse Events
AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Anti-Retroviral Therapy
BMI	Basal Metabolic Index
CHW	Community Health Workers
CI	Confidence Interval
COR	Crude Odds Ratio
CPT	Cotrimoxazole Prophylaxis
DM	Diabetes Miletus
DOT	Direct Observe Therapy
DST	Drug Sensitivity Test
EPHI	Ethiopia Public Health Institution
EPTB	Extra Pulmonary Tuberculosis
ETB	Ethiopian Birr
FMOH	Federal Minister of Health
HAART	Highly Active Anti-Retroviral Therapy
HBCS	High Burden Countries
HCW	Health Care Workers
HIV	Human Immune Deficiency Virus
LUTF	Lost To Follow Up
MAM	Moderate Acute Malnutrition
MDR-TB	Multi Drug Resistance Tuberculosis Bacilli
OIs	Opportunistic Infections
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PTB	Pulmonary Tuberculosis

RR	Rifampicin Resistant
SAM	Severe Acute Malnutrition
SD	Standard Deviation
SLDs	Second Line Drugs
SNNPR	Southern Nation Nationalities and Peoples Region
TB	Tuberculosis Bacilli
TFCs	Treatment Follow Up Centers
TICs	Treatment Initiating Centers
VAS	Visual Analogue Scale
WHO	World Health Organization
XDR	Extensive Drug Resistant

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ABSTRACT

Background: One of the key elements of successful tuberculosis control programs is adherence to treatment, and this is a cornerstone of most international and national policies and guidelines. Few studies had investigated the survival status and factors associated with poor MDRTB treatment outcomes, but there is no published studies that assessed the magnitude and factors associated with MDRTB treatment non-adherence that determine outcomes in the study area. Therefore, the study will give insight on area of focus for program coordinators.

Objective: To assess the level of non-adherence and associated factors among adult MDR-TB Patients attending public health institutions in South Nations Nationalities Peoples Region, Ethiopia

Method: A facility based cross-sectional study design was conducted among adult MDRTB patients who are on follow-up and treatment in public hospitals in South Region from July 16 –August 15/2019. There were 160 MDRTB patients eligible and all were included in the study. Data was collected by trained data collectors using a structured and pre-tested questionnaire. Data was analyzed using SPSS- 25. Bivariate and multivariate logistic regression was fitted to identify predictors and control potential confounding variables. 95% confidence interval and p-value of < 0.05 was considered as cutoff.

Result: Twenty seven (16.9%) of the patients were non-adherent in the last one month. Ten (37%) of patients missed drug doses due to drug adverse events. Distance from health facility (AOR=4.6; CI=1.5-18); lack of adherence care and social support (AOR=5; 95% CI = 1.2 - 21); grade three or more adverse events (AOR=7.7; CI = 2-25); being on long term regimen (AOR=3.8; CI = 2 - 13) and co-morbidities including HIV/AIDS (AOR=4.5; CI= 1.5 - 20) were significantly associated with non-adherence.

Conclusion: Non-adherence to MDRTB treatment was high among patients attending public hospitals in South Nations Nationalities Peoples Region. Non-flexible health delivery and insufficient support system, toxicities associated with drugs for MDRTB and comorbidities independently determine non-adherence. Interventions must be targeted to address these issues.

Key words: Non- Adherence, MDRTB, SNNPR, Ethiopia

1. INTRODUCTION

1.1. Background

Multidrug-resistant Tuberculosis (MDR-TB) is TB that is resistant to both rifampicin and isoniazid, the two most powerful anti-TB drugs; it requires treatment with a second-line regimen(1). MDR-TB is a major public health concern in many countries because of its difficulty in treatment and high costs(2). Drug resistance in *Mycobacterium tuberculosis* may result from two mechanisms: inappropriate treatment regimens, poor quality drugs, and inadequate intake of first line Anti-TB treatment (acquired resistance) or infection with a drug resistant *M. tuberculosis* strain (primary resistance)(3). Globally in 2017, an estimated 3.5% of new cases and 18% of previously treated cases had MDR/RR-TB. There were an estimated 558 000 (range, 483 000–639 000) incident cases of MDR/RR-TB and about 230 000 (range, 140 000–310 000) deaths from MDR/RR-TB in 2017(4). In many countries, one of the barriers to adequate access to treatment of drug-resistant TB is that the network for the programmatic management of drug-resistant TB (PMDT) is too centralized and too reliant on hospital-based models of care. Greater decentralization and more use of outpatient models of care are needed(4). The treatment of MDR TB is lengthy, toxic, expensive, and has generally poor outcomes(5). Inadequate treatment can lead to unfavorable outcomes for the patient, while increasing the risk of transmission and the development of extensive drug resistance(6).

Ethiopia is one of the 30 high TB, TB/HIV and multidrug resistant TB (MDR-TB) burden countries. According to the recent national TB drug resistance surveillance report, 2.3% of new TB cases and 17.8% of previously treated TB cases were estimated to have MDR(7). In 2017, 680 MDR/RR-TB and 4 XDR-TB laboratory-confirmed cases started on treatment(4). Ethiopian Federal Ministry of Health (FMOH) recommends two models of care for management of MDR TB patients : In- Patient and outpatient(8) . In the inpatient model of care, all eligible patients that are ready to start treatment with second line drugs (SLDs) are admitted to treatment initiating centers (TICs) with designated MDRTB wards for four to eight weeks till the patient turn sputum smear negative. Upon discharge from the TICs, patients are referred to treatment follow up centers (TFCs) for out- patient follow up(8). In the ambulatory model of care, patients are treated at outpatient level at TFCs from day one. The multidisciplinary panel team at TICs may recommend

temporary admission at TICs based on clinical or social criteria. At TFCs, patients received daily injections six times per week for the initial 8–9 months (intensive phase) and attended daily follow up during the continuation phase. The patients received their medications under direct observation and strict follow up by health workers both at TICs and TFCs(9).

One of the key elements of successful tuberculosis control programs is adherence to treatment, and this is a cornerstone of most international and national policies and guidelines. Non-adherence is often due to patient-related factors, but can also be a result of provider issues, such as stock-outs of TB medicines(10). Non-adherence results in increases in length and severity of illness, deaths, disease transmission, and drug resistance. These have economic consequences in terms of costs and loss of income for patients and their families and also costs to the health system(11). Non-adherence is commonly due to treatment interruption, which may be for short intermittent periods of a few days or for longer periods of weeks or months, and may even end up as complete discontinuation of treatment. Interventions to prevent treatment interruption are aimed at both patients and providers(12).

1.2. Statement of the problem

Success of treatment relies heavily on adherence, which in turn relies on: good understanding by the patient of the fundamentals of DR TB and its treatment; Commitment from the patient to participate in treatment; support of the patient by the family; and good communication between the provider, the patient, and the family(8). Patient adherence to treatment is multi-factorial and involves individual patient factors, provider factors, and community factors(13).

In Ethiopia the treatment success rate of MDR TB was 75% which was lower than for drug sensitive TB with high rates of treatment failure and default(4,7). Study done in Southern Nation Nationalities and Peoples Region (SNNPR) show that 11% of the MDR TB cases for whom 24 months outcome has been determined and 2.7 % of first line anti- TB drug susceptible cases were LTFU or not evaluated(14). Another study done in the region showed that the low MDRTB treatment success rate may be due to higher loss to follow up rate, in which 13% of patients were either lost to follow up or defaulted which markedly reduces the proportion of successful treatments(15). Treatment for MDR-TB typically utilizes at least five active drugs depending on the specific resistance profile of the infection and includes second-line drugs, which have increased

toxicity, worse side effects, greater treatment burden (e.g. number of pills) and reduced individual efficacy(4,8,16,17). Studies in drug-susceptible TB patients have suggested that treatment interruptions are associated with an increased risk for treatment default, failure, or death(18), but the characteristics and patterns of missed doses and treatment interruptions that are most predictive has not been well established in patients with MDR TB.

1.3. Significance of the study

Few studies had investigated the survival status and factors associated with poor MDRTB treatment outcomes (7,14,15,19), but there is no studies that assessed the magnitude and factors associated with MDRTB treatment adherence in the study area. This study will help addressing issue of non- adherence during MDRTB treatment and it will provide insights on the barriers to successful completion and help providers to identify where support is needed the most and who is at the highest risk of unfavorable outcomes.

2. LITERATURE REVIEW

2.1. Prevalence of non- adherence

Even though there is no study that directly assesses the magnitude of non-adherence to MDRTB treatment in Ethiopia, some studies assess unsuccessful treatment outcomes (default, Lost to Follow-up (LTFU) and death) which are mainly due to non-adherence. A study done in Gonder and Addis Ababa shows 5.9% of lost to follow-up (20) which is lower than the previous reports of 8.9% from northeast Ethiopia (7) and south region of 13% (15), and 14% globally (4). In Kenya, 15.8% patients had been LTFU by 12 months on treatment (21). Non-adherence level within last one month prior to the study was 19.5% in a study done in Addis Ababa consisting of both drug susceptible and drug resistance TB (22). A study done in Philippines indicates only 7.0% of 583 MDRTB patients completed treatment without interruption (23). In Lima and Callao, Peru, the mean treatment non-adherence rate was 24% (24). Another study done in Armenia and Abkhazia, 32.3% of the patients were defaulters which is the highest (25).

2.2. Factors associated with MDRTB treatment non-adherence

2.2.1. Patient related factor

Some of the patient-related factors reported to affect adherence are: forgetfulness; psychosocial stress; anxieties about possible adverse effects; low motivation; inadequate knowledge and skill in managing the disease symptoms and treatment; lack of self-perceived need for treatment; lack of perceived effect of treatment; negative beliefs regarding the efficacy of the treatment; misunderstanding and non-acceptance of the disease; disbelief in the diagnosis; lack of perception of the health risk related to the disease; misunderstanding of treatment instructions; lack of acceptance of monitoring; low treatment expectations; low attendance at follow-up, or at counselling, motivational, behavioral, or psychotherapy classes; hopelessness and negative feelings; frustration with health care providers; fear of dependence; anxiety over the complexity of the drug regimen, and feeling stigmatized by the disease (26).

A study conducted in metropolitan Lima, Peru, history of substance use predicted a significantly higher rate of default (17). A research done in India shows psychiatric disorders were already present in 8 (6.15%) patients before the start of MDR-TB treatment and development of psychiatric disorder in 12 (9.23%) patients after initiation of the treatment. Depressive disorder (6.9%),

anxiety disorder (3.8%) and psychosis (3.1%) were most frequent psychiatric disorders(27). An association was found with the use of Cycloserine and development of Psychosis during the management of patients with MDR-TB done in Nigeria(28) . Low level of Knowledge about DR TB and its treatment(29) ,Age (children, teenagers and the elderly), Low literacy status ,Stigma and discrimination ,Family, community and house hold influence are the main patient related barriers to adherence(30–34). Poor adherence to prescribed regimens affects all age groups. However, the prevalence of cognitive and functional impairments in elderly patients increases their risk of poor adherence. Multiple co-morbidities and complex medical regimens further compromise adherence. Age-related alterations in pharmacokinetics and pharmacodynamics make this population even more vulnerable to problems resulting from non-adherence(26).

2.2.2. Socioeconomic factors

Study findings had highlighted the economic burden due to MDR-TB with issues related to inaccessibility of treatment, distance, transport costs and costs incurred during hospitalization(35). Inability to work due to the side effects of the drugs and therefore loss of income has been a major impediment leading to treatment default(36). World Health Organization(WHO) calculated that the average drug sensitive TB patient loses three to four months of work-time and up to 30% of their household annual earnings(36). Patients and healthcare providers consistently cited financial constraints as the most common barriers to accessing care. Rural residents, farmers and ethnic minorities were the most vulnerable to these barriers, and patients with MDR-TB reported a higher financial burden owing to the centralization and longer duration of treatment. Support in the form of free or subsidized treatment and medical insurance, was deemed essential but inadequate for alleviating financial barriers to patients (37).

MDR-TB has a huge adverse economic impact on patients due to the long duration and complexity of treatment. The socioeconomic barriers include inaccessibility of treatment, distance, transport costs and costs incurred during hospitalization(38). Another study reported that 5/10 patients had not resumed work even after one year of treatment, and at times caregivers also had to stop going to work for months at a time. There was also a reduction in salary due to work absenteeism and some income had to be spent on costs associated with treatment(39).

Cost of treatment or investigations is another economic factor that hinder treatment adherence. A study done in dominical republic shows MDR-TB patients bore a total financial burden of \$412 direct costs and \$3,146 indirect costs (total cost \$3,558). The direct cost for diagnosis was \$154 and for treatment was \$258(40). According to the same study 23% of MDR-TB patients had defaulted on treatment due to financial constraints(40).

2.2.3. Health system-related factors

Whereas a good patient-provider relationship may improve adherence, there are many factors that have a negative effect. These include, poorly developed health services with inadequate or non-existent reimbursement by health insurance plans, poor medication distribution systems, lack of knowledge and training for health care providers on managing chronic diseases, overworked health care providers, lack of incentives and feedback on performance, short consultations, weak capacity of the system to educate patients and provide follow-up, inability to establish community support and self-management capacity, lack of knowledge on adherence and of effective interventions for improving it(26).

A study done in Lima and Callao, Peru, TB services were available for 66 h/day in 55% of the health centers. Community Health Workers(CHWs) supporting DR-TB patients were available at 45% of the health centers(24). Several obstructing system factors were identified such as insufficient access and use of rapid molecular testing, limited expertise and limited sharing of expertise between professionals, lack of treatment guidance and protocols, long duration of hospitalization and difficulties ensuring continuation of treatment and care for patients crossing borders(6).

Access and convenience of services (distance, waiting time, privacy, and confidentiality) are significantly associated with non-adherence. A meta-analysis in Ethiopia shows the final pooled Meta regression analysis showed statistically significant difference between long waiting time CI = 3.44, 6.91) (41). Another factors include Poor condition of the clinic, attitude of health care provider to patient and the disease, low level of knowledge of the Health Care Worker(HCW) about DR TB and treatment and health personnel beliefs (e.g., fear of being infected(8). In another study majorities of patients (57.4%) were not satisfied by the counseling of health care worker(42). A study done in South Africa shows less than half (47.3%) of the participants had a good level of

knowledge about MDR-TB. With regard to practice, about 83% of participants stated that they used protective masks whilst attending to MDR-TB patients. About two-thirds (66.4%) reported being personally involved in educating patients about MDR-TB; whilst about 55% stated that they referred to these guidelines(43).

2.2.4. Treatment- related factors

It is generally known that adherence to MDR-TB treatment is particularly difficult because of the lengthy (20 months or more) treatment duration, the high daily pill burden, adverse drug reactions and failure of previous treatments(44).one MDRTB patient on average need 20 pills and one painful injection per day for a minimum of eight months during the intensive phase and further 20 pills per day for a minimum of 12 months during the continuation phase i.e.240 injections and 12,000 pills despite ancillary medications and treatment for comorbid diseases(45). In MDR/RR-TB patients who have not been previously treated for more than 1 month with second- line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens(1).Attempts to gradually reduce the duration of the regimen to a 9-month regimen with seven agents in a 4-month intensive phase and four agents in a 5-month continuation phase started two decades ago in Bangladesh and stabilized in recent years (46). This regimen, with some variations, was subsequently adopted in other low-resource settings, mostly in Africa. In Ethiopia, the Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB (STREAM) study was conducted to properly evaluate the efficacy of the shorter regimen and started for eligible patients since 2019(47).

Co-morbidities like HIV are major barriers to treatment adherence. A study done in South Africa highlights six-month optimal adherence was higher for Anti-Retro Viral drugs (ARV) (88.2%) than TB medications (67.7%) ($p<0.001$). Low educational attainment, male gender, and year of enrollment were independently associated with dual suboptimal adherence. In the complete case sensitivity analysis, HIV infection was also associated with an unfavorable outcome (48).

In Nepal, as reported by patients 25.74% had missed one or more doses of drugs and 11.5% missed four doses of drugs during last month. Last month 3.9% patients missed drug doses due to side

effects of the drugs .Common side effect reported by patients were joint pain (21.2%), nausea (20.3%) hearing disturbances (11%), and gastrointestinal disturbance (9.9%) (42).

3. CONCEPTUAL FRAME WORKS

This Schematic diagram showed the relationships between independent and dependent variables Independent variables

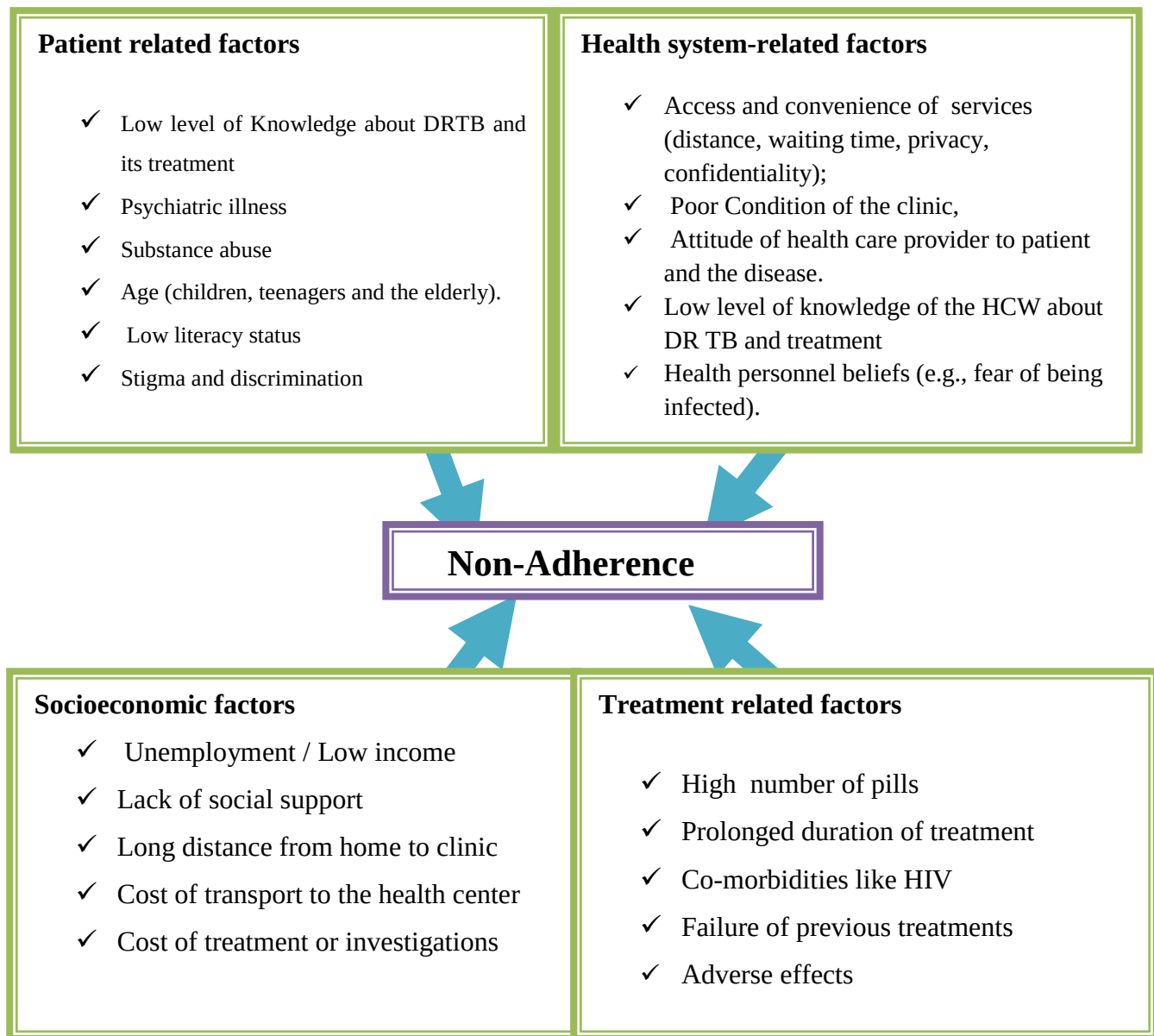


FIGURE 1: CONCEPTUAL FRAME WORK SHOWED RELATIONSHIPS BETWEEN INDEPENDENT AND DEPENDENT VARIABLES

4. OBJECTIVES OF THE STUDY

4.1. General objective

- ❖ To assess the magnitude of non-adherence and associated factors to MDR-TB treatment among adult MDR-TB Patients attending public health institutions in SNNPR , Ethiopia

4.2 .Specific objective

- ❖ To determine the magnitude of non- adherence to treatment among adult MDRTB patients
- ❖ To assess associated factor of non-adherence to treatment among adult MDRTB patients.

5. METHODS

5.1. Study area

The study was conducted in SNNPR which is located in South and South West Ethiopia. Southern Nation Nationalities and Peoples Region (SNNPR) is one of the nine regions in the country located in Southern and South-western part of Ethiopia. Its capital city, Hawassa, is located 272 km from Addis Ababa. It has estimated total population of 19,170,007 of which 9,500,004 are males and 9,670,003 are females; 3,178,000 urban and 15,992,000 rural population in 2017 and covers an area of 110,931 km² which is 10% of the country's total area(49). The region share international boundaries with South Sudan and Kenya. Administratively the region sub divides into 14 zones, 4 Special woredas and 1 city administration. Zones further divided into 136 woredas and 22 town administrations making a total of 158 woredas and towns. There are a total of 4,002 kebeles (3678 rural and 324 Urban), 52 functional hospital (2 referral, 11 General and 39 Primary), 723 Health Centers (24 HCs are NGOs) and 3,835 Health Posts. In general, the hotspot woredas constitutes 51% of the total woredas in region. About 96% of the Health Institutions give TB diagnosis and treatment service (10). As of July 2019 there were six MDR-TB Treatment Initiation Centers (TICs), Yirgalem, Hosanna, Arbaminich, Butajira, Mizan Tepi and Dilla , in the region with 176 patients on active MDR TB treatment.

5.2 Study design

A facility based cross –sectional study design was used

5.3 Study period

The study was conducted from July16 - August 15/2019

5.4 Source population

All adult MDR-TB patients taking treatment in public health Institutions in SNNPR, Ethiopia

5.5 Study population

All adult (≥ 15 years old) selected MDR-TB patients taking treatment in SNNPR during the study period.

5.6 sample size determination

The final sample size is calculated using 13% as prevalence of the overall non adherence rate to MDR-TB treatment (defaulters, LUTF and those not evaluated) from previous study done in the SNNPR(15) with 95 % level of certainty and a maximum discrepancy of 5%. For non-response rate 10% of the calculated sample size was considered and the following single population proportion formula is used to calculate the sample size.

$$n = \frac{(Z^{\alpha/2})^2 P(1-P)}{d^2}$$

Where n= sample size

Z= Standard proportion population at 95% confidence interval (1.96)

P= Estimated proportion of adherence

d= Margin of error (5%)

Sample size, n = [1.96²(1.96)² × 0.13(1-0.13)]/ 0.05² = Give as 174. Since the source population and calculated samples were almost equal and manageable, we had included all 176 patients.

5.7 Sampling technique

All MDRTB patients who are currently on treatment were included

5.8 Inclusion criteria

Age greater than or equal to 15 years old

Taking MDR-TB medication at least for one month prior to the study

Who signed consent form

5.9. Exclusion criteria

Critically ill MDR-TB patient,

Newly started on MDR-TB treatment less than 1 month during the interview period.

5.10 .Variables

5.10.1 Dependent variables

- ✚ Non- adherent to MDR-TB treatment

5.10.2 Independent variables

- ✚ Sociodemographic variables
- ✚ Care and support
- ✚ Knowledge status on MDRTB
- ✚ Monthly Income
- ✚ Pill burden
- ✚ drug side effects and grade of adverse events
- ✚ Cost other than anti MDR-TB drugs
- ✚ Distance and transportation
- ✚ Site and Phase of MDRTB treatment
- ✚ MDR-TB – HIV co-infection
- ✚ Co- morbidity other than HIV
- ✚ Nutritional status
- ✚ Forgetfulness
- ✚ Cigarette smoking, Alcohol drinking, and Chewing chat.

5.10.3 Outcome Variable and its measurement

MDR-TB treatment adherence status was the outcome variable dichotomized as adherent and non-adherent. Interviews was conducted using a structured questionnaire that collect socio-demographic information about the patient and establish the number of times they had missed taking drugs in the last one month prior to the interview. There was also a DOT adherence follow-up chart (observer reported). Information on the length of time any injectable or oral drug administration missing was recorded in the patient charts as part of national standard MDR-TB care. Adherence to TB treatment has been defined variably. WHO defines TB treatment non-

adherence as “patients who did not attend a health facility at the scheduled visit and those who did not take regular medication above 90% of prescribed doses” (26). There are also other definitions referred to as either primary or secondary adherence(50). According to this definition, primary non-adherence is when patients do not even fill a new prescription i.e. do not go for drugs to a health facility in the first place, while secondary non-adherence is when prescriptions are filled but the medication is not taken as prescribed. A more general definition of adherence is described as regular medication intake and attending all follow up medical appointments as per the provided guidelines(51). In line with this definition, missing even one dosage or one follow up visit can be defined as non-adherence. Currently none of the available methods can be considered as a gold standard and the combination of methods is recommended(52).

Therefore, in this study, non-adherent patients were: (1) those admitting to have missed ≥ 1 full dose of MDR-TB medications, or (2) those who scored their adherence level less than 90% by Visual Analogue Scale (VAS), in the last 4 weeks. Non-adherence level was estimated by individual patient themselves, being supported by health care workers and confirmed by DOT adherence follow up chart.

5.11 Data collection procedure and data quality control

Data was collected using semi-structured questioner customized from different literatures, WHO and national MDR-TB treatment guideline and adopted from EDHS modified structure questioner(8). Six data collectors who are health professionals were recruited and a one day training was given on basic principles of data collection, on the questionnaire and how to do other related procedures during data collection by the principal investigator. Primary data was collected by interviewing patients on the TICs clinic days and at TFCs where patients were attended to take their medication and food baskets. The daily drug administration monitoring chart which was filled by the health care worker at the DOTS clinic and patient charts were reviewed to obtain secondary data that cannot be extracted from the patient. MDRTB focal persons at each TIC supervised data collectors and avail patient charts. The research team supervised continuously by the Lead Investigator throughout the data collection period. Spot check visits was done to validate the collected data on a regular basis.

A pretest was done at Alert hospital on 5% of the participants to ensure for the accuracy of responses, language clarity, and appropriateness of data collection tools, estimate the time required and the necessary amendment was considered.

5.12 Data analysis and interpretation of results

After data collection, the data was coded on pre-arranged coding sheet by the investigator and the corresponding code number was written at each questionnaire margin. The data was entered using Epi-Info version 7 and template scheme for data entry was developed and pre tested for ranges, skipping patterns and allowed legal values. Any error was identified before analysis by revising entered data and original data's code number. The final data was exported to SPSS version 25.0 for analysis. Descriptive analysis was done to understand the socio-demographic, economic and clinical characteristics of the respondents. Binary logistic regression model was used and the presence and degree of association between dependent and independent variables measured by bivariable logistic regression using crude odds ratio (COR). To control possible confounding effects and to assess separate effects of variables, multivariable analysis using adjusted odds ratio (AOR) was employed. For both bivariable and multivariable analysis 95% confidence interval (CI) and P-value <0.05 was considered as a cut off point for statistical significance in the final model.

5.13 Standard and Operational Definition

5.13.1 Classification based on drug resistance:

Mono-drug resistance: resistance to one first-line anti-TB drug only.

Poly-drug resistance: resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

Multi-drug resistance: resistance to at least both isoniazid and rifampicin.

Extensive-drug resistance: resistance to any fluoroquinolones and to at least one of three second-line injectable drugs (capreomycin, kanamycin and Amikacin), in addition to multidrug resistance.

Rifampicin resistance (RR-TB): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-drug resistance, multi-drug resistance, poly-drug resistance or extensive drug

resistance. Any patient who falls into one of the above listed types of drug-resistance is considered a DR-TB patient. But emphasis is on RR-TB and MDR TB when it is referred in this document.

5.13.2 Classification of DR TB based on Laboratory Confirmation:

Bacteriologically confirmed DR-TB: refers to those cases with documented laboratory drug sensitivity test (DST) (phenotypic or molecular) results for DRTB or Rifampicin Resistant TB.

Presumptive DR-TB: refers to those cases with no documented DST results but the clinical panel team decided to treat the patient empirically with a course of treatment including SLD based on clinical criteria alone. It includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory. When culture and DST results are available these cases were reclassified as bacteriologically confirmed.

5.13.3 Site of DR-TB disease

Pulmonary DR TB: DR-Tuberculosis involving the lung parenchyma.

Extra- pulmonary TB: DR-Tuberculosis involving organs other than the lungs.

5.13.4 Registration group based on history of anti-TB treatment and treatment outcome

New: A patient who has received no or less than one month of anti-tuberculosis treatment.

Previously treated with First line drugs: a patient who has received first line anti-tuberculosis treatment for four weeks or more.

Previously treated with Second line drugs: a patient who has received second-line anti-tuberculosis treatment for four weeks or more.

Relapse: A patient who was previously treated for TB and whose most recent treatment outcome was “cured” or “treatment completed”, and who is subsequently diagnosed with recurrent episode of TB.

Treatment after being lost to follow-up: A patient after taking treatment for more than one month who returns to treatment following interruption of treatment for two or more consecutive months.

Treatment after failure of New TB regimen: A patient who has received new regimen for TB and in whom treatment has failed. Failure is defined as sputum smear/culture positive at five months or later during treatment.

Transfer in: A patient who has been transferred from another TIC to continue MDR-TB treatment.

Other: refers to any DR-TB patient who does not fit into any of the above categories.

5.13.5 Definitions of sputum and culture conversion and reversion

Conversion: is defined as two sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. The date of collection for the first sample is considered as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

5.13.6. Definitions of DR-TB Treatment outcomes

Cured: Treatment completed according to national recommendation without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment completed: Treatment completed according to national recommendation without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: - lack of conversion by the end of the intensive phase, or - bacteriological reversion in the continuation phase after conversion to negative after intensive phase, or - evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs, or adverse drug reactions

Lost To Follow Up (LFTU): A patient whose treatment was interrupted for two consecutive months or more.

Died: A patient who dies for any reason during the course of treatment.

Not evaluated: A patient for whom no treatment outcome is assigned either due to being transferred out to other facility or still on treatment.

5.13.7 Definition of adverse drug events

Grade 1: mild (no modification or discontinuation of drugs)

Grade 2: moderate which leads to temporary discontinuation of the drug/s

Grade 3: severe which led to the medicine being stopped permanently

Grade 4: life threatening or disabling

Grade 5: death related to adverse events

5.13. 8 Definition of nutritional status (BMI)

Normal: 18.5 - 25

Moderate Acute Malnutrition (MAM) : <18.5- 16

Severe Acute Malnutrition (SAM): < 16

5.13.9 Operational definitions

Adult: Age greater than or equal to 15 years old were considered as adults for this study

Self-reported non-adherence: defined as admitting to have missed ≥ 1 dose of MDR-TB medication in the last 4 weeks by questionnaire

Substance use: previous or current use of at least one of alcohol, cigarette, chat, shisha, marijuana

MDRTB knowledge: patients classified as having knowledge if answer ≥ 3 three questions

5.14 Ethical consideration

Ethical clearance was obtained from Ethical review committee of St. Paul's Hospital Millennium Medical College Department of Public Health and authority to collect was obtained from SNNPR Health Bureau and submitted to the respective health facilities. Patients and parents for those under 18 years signed their informed consent prior to the start of the interviews. Participating in this study had no any risk or harm .The final data set obtained did not contain any information that can be used to identify respondents such as names. Research assistants was properly trained on issues of confidentiality and high levels of data security was maintained.

5.15 Dissemination of results

The final result will be submitted to St. Paul's Hospital Millennium medical college department of public health, SNNPR Health Bureau, each TICs and TFCs and other responsible bodies and Stakeholders working on the study area. The findings of the study will be published and disseminated through journals and scientific conferences

6. RESULTS

6.1. Sociodemographic and Clinical Characteristics of Participants

Among the 176 MDRTB patients in the Region who were on active treatment during the study period, 7 were under fifteen years, 5 were on treatment for less than a month, 2 were critically ill and 162 were eligible for the study and 160 (98.8%) of the eligible participant responds to the interview.

The minimum, maximum and the mean age of the participants was 14, 82 and 29.9 ± 12 SD years respectively. Sixty three (39.4%) of them were between the age of fifteen and twenty four years. 12(7.5%) of the patients in the age group of 25- 34 were non-adherent. Males accounted for 103(64.4%) of the participants. Among the study participants, 82(51.2%) of them were married; 65(40.6%) attended primary education; 124(77.5%) live in rural area; (35.6%) were farmers and 76 (47.5%) claim that their average monthly income was 1000 or less ETB (table 1).

TABLE 1: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF MDRTB PATIENTS, SNNPR, ETHIOPIA, 2019

Variables	Category	Non-adherent	
		Yes N (%)	No N (%)
Age	15- 24	8(5.0)	55(34.4)
	25 - 34	12(7.5)	39(24.4)
	35 - 44	4(2.5)	21(13.1)
	≥45	3(1.9)	18(11.3)
Sex	Male	22(13.8)	81(50.6)
	Female	5(3.1)	52(32.5)
Religion	Orthodox	6(3.8)	26(16.3)
	Protestant	16(10.0)	96(60.0)
	Muslim	5(3.1)	12(7.5)
Marital status	Single	12(7.5)	60(37.5)
	Divorced/ widowed	1(0.6)	5(3.1)
	Married	14(8.8)	68(42.5)

Level of education	None	11(6.9)	37(23.1)
	Primary	11(6.9)	54(33.8)
	Secondary	3(1.9)	39(24.4)
	Tertiary	2(1.3)	3(1.9)
Residence	Urban	2(1.3)	34(21.3)
	Rural	25(15.6)	99(61.9)
Occupation	Unemployed	1(0.6)	4(2.5)
	House wife	2(1.3)	27(16.9)
	Government employee	2(1.3)	5(3.1)
	Private employee	2(1.3)	23(14.4)
	Farmer	13(8.1)	44(27.5)
	Daily laborer	2(1.3)	4(2.5)
	Student	5(3.1)	26(16.3)
Average monthly income(ETB)	No income(dependent)	1(0.6)	4(2.5)
	<1000	11(6.9)	65(40.6)
	1000-2000	12(7.5)	45(28.1)
	>2000	3(1.9)	19(11.9)

All the patients undergo treatment through DOTS programme and got monthly food -basket and compensation for transportation cost during TIC visit. MDRTB status was disclosed to the family in all patients. The DOTS center was located at 5 km or less in 137(85.7%) of the participants. Adherence care and social support provided for 143(89.4%) of the participants. One hundred fifteen patients (71.9%) had previously treated for tuberculosis and among them 7 (6%) were treatment after LTFU. Patients taking short term drug regimen were 88(55%). One or more drug adverse effect was observed in 94(59%) of the patients and these adverse events lead to suspension of at least one drug in 29(18.1%) of them. Twenty seven (16.9%) of the patients had either previous or current history of substance use and among them 19(70%) used chat. HIV test was done for all MDRTB patients and **9(5.6%)** of them were positive and ART started for all of them. In this study, 59(36.9%) of the patients had normal BMI whereas 30(18.8%) of them had severe malnutrition (table 2).

TABLE 2: HEALTH CARE SYSTEM, CLINICAL AND PATIENT RELATED FACTORS, SNNPR, ETHIOPIA, 2019

Variables		Non-adherence	
		Yes	No
Distance from health facility	≥5km	9(6.1%)	14(8.8%)
	<5km	18(11.3%)	119(74.4%)
Availability of transport	No	14(8.8%)	85(53.1%)
	Yes	13(8.1%)	48(30.0%)
Transportation cost per day(ETB)	>10	3(1.9%)	9(5.6%)
	5-10	8(5.0%)	21(13.1%)
	<5	3(1.9%)	19(11.9%)
	None	13(8.1%)	84(52.5%)
Waiting time	≥30min	4(2.5%)	7(4.4%)
	<30min	23(14.4%)	126(78.8%)
Site of treatment	TIC	7(4.4%)	10(6.3%)
	TFC	20(12.5%)	123(76.9%)
Health education	No	4(2.5%)	21(13.1%)
	Yes	23(14.4%)	112(70.0%)
Adherence care and social support	No	8(5.0%)	9(5.6%)
	Yes	19(11.9%)	124(77.5%)
Availability of drugs	Some drugs	9(5.6%)	11(6.9%)
	Always	18(11.3%)	122(76.3%)
Grade 3 or 4 AEs	Yes	14(8.8%)	15(9.4%)
	No	13(8.1%)	118(73.8%)
Type of drug regimen	Long term	19(11.9%)	53(33.1%)
	Short term	8(5.0%)	80(50%)
Substance use	Yes	11(6.9)	16(10.0)
	Never	16(10.0)	117(73.1)

Knowledge of MDRTB	No	12(7.5)	32(20.0)
	Yes	15(9.4)	101(63.1)
Comorbidity including HIV/AIDS	Yes	7(4.4)	13(8.1)
	No	20(12.5)	120(75.0)
Nutritional status(BMI)	SAM	11(6.9)	19(11.9)
	MAM	10(6.3)	61(38.2)
	Normal	6(3.8)	53(33.1)

6.2 Magnitude of MDRTB treatment non-adherence

Twenty seven (16.9%) of the patients who currently on treatments had history of MDRTB treatment non-adherence in the last month. Ten (37%) of patients missed drug doses due to drug adverse events (Table3).

TABLE 3. CAUSES OF MDRTB TREATMENT NON-ADHERENCE AMONG PATIENTS CURRENTLY ON TREATMENT IN SNNPR, ETHIOPIA, 2019

Reason for missing treatment	Frequency(n=27)	Percent
Adverse events	10	37
Stock out of drug	7	26
Pill burden and fear of side effect	6	22
Distance of the health facility	6	22
Felling healthy and cured	4	15
Overlapping of working hour and medication time	2	7.5
Forgetfulness	1	3.5

6.3. Simple Logistic Regression of Factors (Bivariate Analysis)

6.3.1. Sociodemographic Factors

Among the Sociodemographic factors, only sex has statistically significant association with MDRTB treatment non-adherence (Table 4).

TABLE 4. SOCIO-DEMOGRAPHIC CHARACTERISTICS AND THEIR ASSOCIATION WITH NON-ADHERENCE AMONG MDRTB PATIENTS IN SNNPR, ETHIOPIA, 2019

Variables	Category	Non-adherent		COR(CI)	P-VALUE
		Yes	No		
Age	15- 24	8	55	Ref.	0.49
	25 - 34	12	39	2.1(0.8,5.7)	0.14
	35 - 44	4(2.5)	21	1.3(0.36,4.8)	0.69
	≥45	3	18	1.2(0.27,4.8)	0.85
Sex	Male	22	81	2.8(1.01,7.9)	0.049*
	Female	5	52	Ref.	Ref.
Religion	Orthodox	6	26	Ref.	0.31
	Protestant	16(10.0)	96(60.0)	0.7(0.26,2)	0.55
	Muslim	5(3.1)	12(7.5)	1.8(0.46,7)	0.40
Marital status	Single	12(7.5)	60(37.5)	0.98(0.4,2.3)	0.95
	Divorced/ widowed	1(0.6)	5(3.1)	1.2(0.13,11.7)	0.88
	Married	14(8.8)	68(42.5)	Ref.	0.99
Level of education	None	11(6.9)	37(23.1)	Ref.	0.18
	Primary	11(6.9)	54(33.8)	0.7(0.3,1.7)	0.43
	Secondary	3(1.9)	39(24.4)	0.3(0.1,1)	0.06
	Tertiary	2(1.3)	3(1.9)	2(0.3,15)	0.41
Residence	Urban	2(1.3)	34(21.3)	Ref.	
	Rural	25(15.6)	99(61.9)	4.3(0.97,19)	0.056
Occupation	Unemployed	1(0.6)	4(2.5)	Ref.	0.41
	House wife	2(1.3)	27(16.9)	0.3(0.02,4)	0.36
	Government employee	2(1.3)	5(3.1)	1.6(0.1,24.7)	0.74

	Private employee	2(1.3)	23(14.4)	0.35(0.25,4.8)	0.43
	Farmer	13(8.1)	44(27.5)	1.2(0.12,12)	0.89
	Daily laborer	2(1.3)	4(2.5)	2(0.13,32)	0.62
	Student	5(3.1)	26(16.3)	0.8(0.07,8)	0.83
Average monthly income(ETB)	No income	1(0.6)	4(2.5)	Ref.	0.75
	<1000	11(6.9)	65(40.6)	0.68(0.07	0.74
	1000-2000	12(7.5)	45(28.1)	1.1(0.12,10)	0.96
	>2000	3(1.9)	19(11.9)	0.6(0.05,7.75)	0.72

6.3.2. Health Care System and Disease Related Factors

On bivariate analysis, distance of the DOTs clinic, adherence care and social support, availability of MDRTB drugs, Type of MDRTB drug regimen and presence of grade three or more AE was significantly associated with treatment non-adherence (Table 5).

TABLE 5. HEALTH CARE SYSTEM AND DISEASE RELATED FACTORS AND THEIR ASSOCIATION WITH NON-ADHERENCE AMONG MDRTB PATIENTS IN SNNPR, ETHIOPIA, 2019

Variables		Non-adherence		COR(CI)	P-value
		Yes	No		
Distance from health facility	≥5km	9(6.1%)	14(8.8%)	4(2,11)	0.004*
	<5km	18(11.3%)	119(74.4%)	Ref.	Ref.
Availability of transport	No	14(8.8%)	85(53.1%)	Ref.	
	Yes	13(8.1%)	48(30.0%)	1.6(0.7,3.8)	0.24
Transportation cost per day(ETB)	>10	3(1.9%)	9(5.6%)	2(0.5,9)	0.29
	5-10	8(5.0%)	21(13.1%)	2.5(0.9,6.7)	0.08
	<5	3(1.9%)	19(11.9%)	1.1(0.25,4)	0.98
	None	13(8.1%)	84(52.5%)	Ref.	0.29
Waiting time	≥30min	4(2.5%)	7(4.4%)	3(0.8,11)	0.087
	<30min	23(14.4%)	126(78.8%)	Ref.	

Site of treatment	TIC	7(4.4%)	10(6.3%)	4.3(1.5,12)	0.008*
	TFC	20(12.5%)	123(76.9%)	Ref.	
Health education	No	4(2.5%)	21(13.1%)	1.1(0.3,3)	0.899
	Yes	23(14.4%)	112(70.0%)	Ref.	
Adherence care and social support	No	8(5.0%)	9(5.6%)	5.8(2,17)	0.001*
	Yes	19(11.9%)	124(77.5%)	Ref.	
Availability of drugs	Some drugs	9(5.6%)	11(6.9%)	6(2,15)	0.001*
	Always	18(11.3%)	122(76.3%)	Ref.	
Grade 3 or 4 AEs	Yes	14(8.8%)	15(9.4%)	8.5(3.4,21.4)	<0.001*
	No	13(8.1%)	118(73.8%)	Ref.	
Type of drug regimen	Long term	19(11.9%)	53(33.1%)	3.5(1.3,8.7)	0.005*
	Short term	8(5.0%)	80(50%)	Ref.	

Gastrointestinal disturbance was the most common adverse event observed in 39(41.5%) of the patients (figure 2).

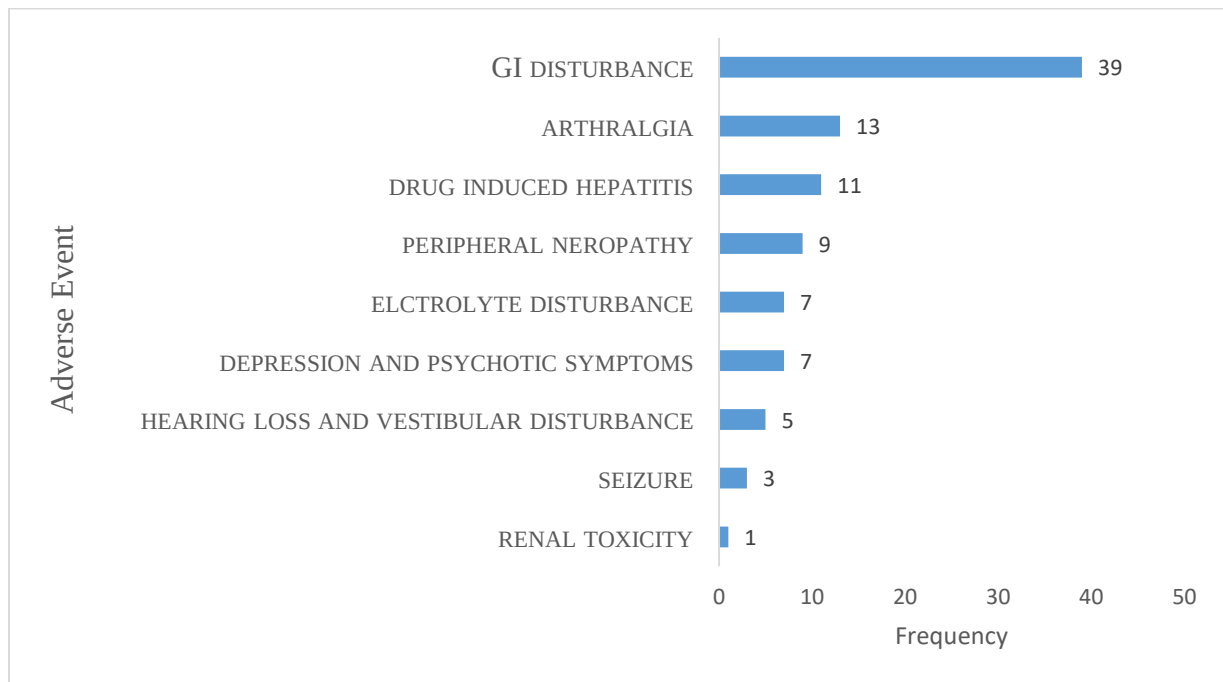


FIGURE 2. TREATMENT ADVERSE EVENTS AMONG MDRTB PATIENTS IN SNNPR, ETHIOPIA, 2019

6.3.3. Patient related factors

Substance use, comorbidity including HIV/AIDS and nutritional status of the patient was significantly associated with treatment non-adherence (table 6).

TABLE 6. PATIENT RELATED FACTORS AND THEIR ASSOCIATION WITH NON-ADHERENCE AMONG MDRTB PATIENTS IN SNNPR, ETHIOPIA, 2019

Variables	Category	Non-adherence		COR(CI)	P-value
		Yes (%)	No (%)		
Substance use	Yes	11(6.9)	16(10.0)	5(2,12.7)	0.001*
	Never	16(10.0)	117(73.1)	Ref.	
Knowledge of MDRTB	No	12(7.5)	32(20.0)	2.5(0.8,5.9)	0.054
	Yes	15(9.4)	101(63.1)	Ref.	
Comorbidity including HIV/AIDS	Yes	7(4.4)	13(8.1)	3(1.5,9)	0.026*
	No	20(12.5)	120(75.0)	Ref.	
Nutritional status(BMI)	SAM	11(6.9)	19(11.9)	5(1.7,15.7)	0.004*
	MAM	10(6.3)	61(38.2)	1.5(0.5,4.3)	0.50
	Normal	6(3.8)	53(33.1)	Ref.	0.008*

6.4 Multivariate Analysis of Factors Associated With MDRTB Treatment Non-Adherence

After adjusted for possible cofounders in the multiple logistic regression, distance from health facility, presence of adherence care and social support, grade three or more adverse events and comorbidities including HIV/AIDS had statistically significant association with MDRTB treatment non-adherence.

Participants whose residence located 5 km or more from the health facility (DOTs center) were 4.6 times more likely to be non-adherent than those participants whose residence was located less than 5 km from the DOTs center ($p=0.034$; 95% CI=1.5 to 18). MDRTB patients who had no adherence care and social support were 5 times more likely to be non-adherent than patients who had adherence care and social support ($p = 0.029$; 95% CI = 1.2 to 21). The occurrence of grade three or more adverse events increased the likelihood of treatment non-adherence by 7.7 times ($p = 0.001$; CI = 2 to 25). MDRTB Patients on long term regimen were 3.8 times more likely to be non-adherent than those on short term regimen ($p = 0.035$; CI = 2 to 13). Similarly, the presence of comorbidities including HIV/AIDS increased the chance of being non-adherent by 4.5 times ($p = 0.04$; CI= 1.5 to 20) (table 7).

TABLE 7. MULTIPLE LOGISTIC REGRESSION OF SELECTED FACTORS ASSOCIATED WITH MDRTB TREATMENT NON-ADHERENCE AMONG MDRTB PATIENTS IN SNNPR, ETHIOPIA, 2019

Variables	Category	COR(CI)	AOR(CI)	P-value
Sex	male	2.8(1.01,7.9)	2.5(0.7,9)	0.17
	Female	Ref.	Ref.	Ref.
Distance from health facility	≥5kms	4(2,11)	4.6(1.5,18)	0.034*
	<5kms	Ref.	Ref.	Ref.
Site of treatment	TIC	4.3(1.5,12)	2(0.4,9.6)	0.40
	TFC	Ref.		
Adherence care and social support	No	5.8(2,17)	5(1.2,21)	0.029*
	Yes	Ref.	Ref.	
Availability of drugs	Some drugs	6(2,15)	1.3(0.2,5)	0.88
	Always	Ref.	Ref.	
≥Grade 3 AEs	Yes	8.5(3.4,21.4)	7.7(2,25)	0.001*
	No	Ref.	Ref.	
Type of drug regimen	Long term	3.5(1.3,8.7)	3.8(2,13)	0.035*
	Short term	Ref.	Ref.	
Substance use	Yes	5(2,12.7)	2.2(0.6,9)	0.25
	Never	Ref.	Ref.	
Comorbidity including HIV/AIDS	Yes	3(1.5,9)	4.5(1.5,20)	0.04*
	No	Ref	Ref.	
Nutritional status(BMI)	SAM	5(1.7,15.7)	4(0.9,18)	0.06
	MAM	1.5(0.5,4.3)	1.5(0.4,6)	0.6
	Normal	Ref.	Ref.	Ref.

7. DISCUSSION

In this study, the magnitude of non-adherence was found to be 16.9% which was lower than a 19.5% finding a study done in Addis Ababa consisting of both drug susceptible and drug resistance TB(22) and a 24% finding in Peru(24). A study done in Nepal showed, 25.74% patients missed one or more doses of drugs which was higher than the finding of this study(42). A study done in Kenya established that the proportion of the patients found to be non-adherent was 35%(53). This variation could be due to different definition of no adherence and method of reporting (self-reported or observer reported). It is possible that self-reported adherence figures are an over-estimate since patients may be hesitant to report the extent of their non-adherence to study staff in non- DOT programs. Thus, Lack of consistent definition of what adherence to treatment is makes it difficult to compare results of studies. Other factors that affect the result are residence (rural, urban), type and duration of MDRTB regimens.

According to the finding of this study, distance from DOTS clinic to patient home independently associated with treatment interruption which is in line with large volumes of research findings that witnessed as still patients from developing countries were interrupting their treatment due distance from treatment center to their home and fear of lost wages or employment for those who travel to treatment centers on a regular basis(46,54–58). In this study, majority of the patients were from rural area where the availability and affordability of transportation was difficult. For many patients who were already suffering from severe weight loss and physical malaise, this means going to the DOT clinics on foot which is physically demanding and they may opt not go to the follow up centers. In this study, all of the patients were under DOT and health staff are often the suggested option, while trained community workers or family members may act as alternatives. However, the beneficial effects of DOT are unlikely to be related to DOT alone; they are also associated with the patient support and supervision activities that come with DOT(46). A review of MDR-TB cohorts also found that family member or community health worker DOT was associated with the lowest default rate(59).

Another factor that significantly affected level of adherence was adherence care and social support. A cross sectional study done in India showed providers related that motivational counselling, nutritional support, family support and social support encouraged treatment adherence(60). Based

on a systematic review from Iran, the main factors associated with TB treatment non-adherence and lost to follow up were socioeconomic factors: lack of transportation cost, lack of social support, and patients-health care worker poor communication(61). A study done in Russia indicated that social support reduced the default outcome (OR 0.13; 95% CI 0.06–0.28)(62).The best practices identified on the ten initiatives on the provision of social support strongly suggest that psycho-socio-economic support interventions can add significant value to TB control through improvements in treatment success rates and reductions in patient suffering. Several programs considered cash payments an effective tool to promote adherence(63). Among the patients included in the psycho-social support program, no treatment default was observed and only one patient missed doses of treatment and interruptions of treatment for at least one day decreased from 18% to 4% among all MDR-TB patients in Kazakhstan(63).

One of the finding of this study was that adverse drug events (especially grade three and more) were an important barrier for treatment adherence which was consistent with previous studies from a Drug Resistant TB Centre in India(2), Girum et al in Ethiopia(15), Williams et al (64). A systematic review and meta-analysis of published literature found that 57.3% of included patients had experienced at least one type of AEs, including mild to severe events 24% (95% CI: 21%–27%) of patients experienced at least one severe AEs during drug-resistant TB treatment that lead to clinician or patient interrupting, stopping or reducing the dosage of treatment before completion(65).

The likelihood of being non-adherent was higher in patients with long term regimens than the short course MDRTB regimens. This finding was consistent with previous studies(47,66,67). This could be due to the shorter treatment duration and pill burden, an earlier return of the patient to work and social activity and reducing the cost of drugs and material support given to the patient from tuberculosis treatment program and releasing more resources to cover the care of more patients thereby facilitating adherence.

In this finding the combined effects of comorbidities found to be strongly associated with MDRTB treatment non-adherence which was in line with the finding of other studies(68–70). Systematic review done in Ethiopia(71) and retrospective cohort study in china(72) showed that patients with MDR-TB and a comorbidity of DM had a significantly lower treatment success rate than those

without DM (36.0 vs. 47.2%, $p = 0.002$). Sequel of diabetes may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. However we combined all comorbidities because data was not sufficient to perform regression for each of them. Similarly studies done reported higher unfavorable treatment outcome which were mainly due to non-compliance in patients with co-morbidities(15,73–75). HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reaction increases with the degree of immune-suppression. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects and non-adherence.

Strength and Limitation of the Study

Strength of the Study

It is probable that self-reported adherence figures are an over-estimate since patients may be hesitant to report the extent of their non-adherence to study staff, we cross -checked the daily drug administration monitoring chart which was filled by the health care worker at the DOTS clinic. This is the first study in the region since the introduction of short term regimens that showed the advantage of the short term regimen over long term regimen in terms of adherence.

Limitation of the Study

The study was subject to a number of limitations. One of the limitations of this study was that Self-report of adherence to medications could also be affected by recall bias. The nature of cross-sectional study design does not indicate temporal relationship or causality. We did not include lost to follow ups.

8. CONCLUSION AND RECOMMENDATIONS

8.1 Conclusion

The study concludes that Non- adherence to MDRTB drugs was high among patients attending public hospitals in SNNPR. Non-flexible health delivery and insufficient support system, toxicities associated with drugs for MDRTB and long duration of treatment and comorbidities like HIV and DM independently determine non-adherence. Interventions must be targeted to address these issues.

8.2 Recommendations

- ✚ National TB program should consider DOT by introducing more flexible health care delivery packages to support patient- centered treatment through health facility based DOT, workplace DOT, guardian-based DOT (by a home-based supporter), or other community based DOT, supervised by a trained community health worker.
- ✚ National TB program and stakeholders should consider introducing electronic and mobile health interventions like Short Messaging Services (SMS) reminders and medication monitors to help support patient adherence
- ✚ Initial assessment of all MDR-TB patients by social workers, including individual counseling on adherence, implications of treatment and treatment duration, support structures, income and care of dependents
- ✚ The coordination of social support from local government (municipalities and districts), and close collaboration between health care professionals, community leaders and religious leaders
- ✚ TICs and TFCs must develop strategies for initial assessment of comorbidities, manage and set strict follow-up and the timely and aggressive management of drug side effects
- ✚ Strengthen availability and use of shorter MDRTB regimens and prevent the acquisition of additional resistance through careful selection of patients to be enrolled, preferably by using in vitro testing with molecular or phenotypic methods, and effective patient support to enable full adherence to treatment.
- ✚ Further research to address lost to follow-ups

9: REFERENCES

1. WHO. WHO treatment guidelines for drug- resistant tuberculosis, 2016 update. 2nd ed. Geneva, Switzerland; 2016.
2. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas A, Kumar AMV, Satyanarayana S et al. Patient and Provider Reported Reasons for Lost to Follow Up in MDRTB Treatment : A Qualitative Study from a Drug Resistant TB Centre in India. PLoS One. 2015;10(8):1–11.
3. Nsofor CA, Jiang Q, Wu J, Gan M, Liu Q, Zuo T, et al. Transmission is a Noticeable Cause of Resistance Among Treated Tuberculosis Patients in Shanghai ,China. J Sci Reports [Internet]. 2017;7(July):7691–7. Available from: <http://dx.doi.org/10.1038/s41598-017-08061-3>
4. WHO. GLOBAL TUBERCULOSIS REPORT 2018. Geneva; 2018.
5. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes : An Individual Patient Data Meta-analysis of 9 , 153 Patients. PLOS Med. 2012;9(8):1–16.
6. European Centre for Disease Prevention and Control (ECDC). Healthcare system factors influencing treatment results of patients with multidrug-resistant tuberculosis. Stockholm; 2014.
7. Baye AM, Sarhie WD, Endalew BT. Treatment Outcomes of Multi-Drug-Resistant Tuberculosis and Its Determinants in Boru Meda Hospital , Northeast Ethiopia. J Infect Dis Ther. 2018;6(1):350–5.
8. FMOH. GUIDELINES ON PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA. second ed. Addis Ababa; 2014. 69–79 p.
9. Habte D, Hiruy N, Melese M, Molla Y, Gashu Z, Jerene D, et al. The experience of scaling up a decentralized, ambulatory model of care for management of multidrug-resistant tuberculosis in two regions of Ethiopia. J Clin Tuberc Other Mycobact Dis [Internet]. 2017;7:28–33. Available from: <http://dx.doi.org/10.1016/j.jctube.2017.03.001>

10. Edine W. Tiemersma, David Collins S van den H. The Economic Cost of Non-adherence to TB Medicines Resulting from Stock-outs and Loss to Follow-up in Kenya;SIAPS RESEARCH SUMMARY. Vol. 3. Arlington, VA; 2017.
11. Collins, D., Demissew Beyene YT et ai. Costs faced by multi-drug resistant tuberculosis patients during diagnosis and treatment . Report from a pilot study in Ethiopia. Addis Ababa; 2014.
12. Hoorn R Van, Jaramillo E, Collins D, Gebhard A, Hof S Van Den. The Effects of Psycho-Emotional and Socio- Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes – A Systematic Review and Meta- Analysis. PLoS One. 2016;11(4):1–27.
13. Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK. Loss-To-Follow-Up on Multidrug Resistant Tuberculosis Treatment in Gujarat , India : The WHEN and WHO of It. PLoS One. 2015;10(7):1–10.
14. Gizaw T. and Andamlak G. TRENDS OF TUBERCULOSIS CASE DETECTION AND TREATMENT OUTCOMES IN SNNPR, ETHIOPIA: RETROSPECTIVE CROSS-SECTIONAL STUDY. In: world tb day and trac. 2017. p. 38.
15. Girum T, Tariku Y DS. Survival Status and Treatment Outcome of Multidrug Resistant Tuberculosis (MDR-TB) among Patients Treated in Treatment Initiation Centers (TIC) in South Ethiopia : A Retrospective Cohort Study. Ann Med Heal Sci Res. 2017;7:331–6.
16. Biadlegne F, Sack U, Rodloff AC. Multidrug-resistant tuberculosis in Ethiopia : efforts to expand diagnostic services , treatment and care. Antimicrob Resist Infect Control. 2014;3:31.
17. Franke MF, Appleton SC, Bayona J, Arteaga F, Llaro K, Shin SS, et al. Risk Factors and Mortality Associated with Default from Multidrug-Resistant Tuberculosis Treatment. 2009;46(12):1844–51.
18. Mesfin MM, Newell JN, Walley JD, Gessesew A, Tesfaye T. Quality of tuberculosis care and its association with patient adherence to treatment in eight Ethiopian districts. Health Policy Plan. 2009;24:457–66.
19. Mesfin YM, Hailemariam D, Biadgign S, Kibret KT. Association between HIV / AIDS and

- Multi-Drug Resistance Tuberculosis : A Systematic Review and Meta- Analysis. PLoS One. 2014;9(1):1–9.
20. Meressa D, Hurtado RM, Andrews JR, Diro E, Abato K, Daniel T, et al. Achieving high treatment success for multidrug- resistant TB in Africa : initiation and scale-up of MDR TB care in Ethiopia — an observational cohort study. *Thorax*. 2015;70:1181–8.
 21. Hirasen K, Berhanu R, Evans D, Rosen S, Sanne I LL. High rates of death and loss to follow-up by 12 months of rifampicin resistant TB treatment in South Africa. PLoS One. 2018;13(10):1–13.
 22. Tola HH, Garmaroudi G, Shojaeizadeh D, Tol A, Yekaninejad MS, Ejeta LT, et al. The Effect of Psychosocial Factors and Patients’ Perception of Tuberculosis Treatment Non-Adherence in Addis Ababa, Ethiopia. *Ethiop J Health Sci*. 2017;27(5):447–58.
 23. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of Treatment Interruption among Patients with Multidrug-Resistant TB (MDR TB) and Association with Interim and Final Treatment Outcomes. PLoS One. 2013;8(7):1–8.
 24. Weiner BJ, Wiesen CA, Lich KLH, Rie A Van, Paul JE, Tovar MA. Innovative approach to the design and evaluation of treatment adherence interventions for drug-resistant TB. *INT J TUBERC LUNG DIS*. 2017;21(11):1160–6.
 25. Bastard, M; Sanchez-Padilla, E; Hewison, C; Hayrapetyan, A; Khurkhumal, S; Varaine, F; Bonnet M. Effects of Treatment Interruption Patterns on Treatment Success Among Patients With Multidrug-Resistant Tuberculosis in Armenia and Abkhazia. *J Infect Dis*. 2014;
 26. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva; 2003.
 27. Kumar A, Chaudhari D, Anand R, Verma SK, Kumar A, Chaudhri S. Occurrence of psychiatric disorders in the patients of multi drug resistant tuberculosis under treatment. *Int J Res Med Sci*. 2018;6(11):3538–41.
 28. Dunga J.A.Datonye Dennis Alasia, Nura Hamidu Alkali. et al. Cycloserine Induced Psychosis among Patient ’ s on Second Line Treatment for Drug Resistant Tuberculosis in Bauchi andPort Harcourt, Nigeria. *Niger Heal J*. 2015;15(3):118–24.

29. Bam TS, Gunneberg C, Chamroonsawasdi K, Bam DS, Aalberg O, Kasland O, et al. Factors affecting patient adherence to DOTS in urban Kathmandu , Nepal. *INT J TUBERC LUNG DIS*. 2006;10(3):270–6.
30. Centre for Disease Prevention and Control. *NATIONAL ACTION PLAN FOR COMBATING MULTIDRUG-RESISTANT TUBERCULOSIS*. Atlanta; 2017.
31. Podewils LJ, Gler MTS, Quelapio MI, Chen MP. Patterns of Treatment Interruption among Patients with Multidrug-Resistant Patterns of Treatment Interruption among Patients with Multidrug-Resistant TB (MDR TB) and Association with Interim and Final Treatment Outcomes. *PLoS One*. 2015;8(7):1–9.
32. Falzon D, Schünemann HJ, Harausz E, González-angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. 2017; Available from: <http://dx.doi.org/10.1183/13993003.02308-2016>
33. Wei X, Yin J, Zou G, Zhang Z, Walley J, Harwell J, et al. Treatment interruption and directly observed treatment of multidrug-resistant tuberculosis patients in China. *INT J TUBERC LUNG DIS*. 2015;19(4):413–9.
34. Kiplangat R, Sang A, Obwoye RO, Kangethe S, Ayiro LP. Patient Factors Which Contribute to Non-adherence to TB Treatment in Kericho and Nakuru Counties of Kenya. *Sci J Public Heal*. 2017;5(4):329–34.
35. Carol D. Hamilton. *Barriers to Global TB Control. THE SCIENCE OF IMPROVING LIVES*. DUKE; 2012.
36. Mishra P, Hansen EH, Sabroe S, Kafle KK. Socio-economic status and adherence to tuberculosis treatment : a case-control study in a district of Nepal. *INT J TUBERC LUNG DIS*. 2005;9(10):1134–9.
37. Hutchison C, Khan MS, Yoong J, Lin X, Coker RJ. Financial barriers and coping strategies : a qualitative study of accessing multidrug- resistant tuberculosis and tuberculosis care in Yunnan , China. *BMC Public Health*. 2017;17:221.
38. Horter S, Stringer B, Reynolds L, Shoaib M, Kasozi S, Casas EC, et al. “ Home is where the patient is ” : a qualitative analysis of a patient-centred model of care for multi-drug resistant tuberculosis. *BMC Health Serv Res* [Internet]. 2014;14(1):1–8. Available from:

39. Sharma R, Yadav R, Sharma M. Quality of Life of Multi Drug Resistant Tuberculosis Patients : a Study of North India. *Acta Med Iran*. 2014;52(6):448–53.
40. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients : A Systematic Review. *PLoS One*. 2016;11(1):1–15.
41. Zegeye A, Dessie G, Wagnaw F, Gebrie A, Islam SMS, Tesfaye B et al. Prevalence and determinants of anti- tuberculosis treatment non-adherence in Ethiopia : A systematic review and meta- analysis. *PLoS One*. 2019;14(1):1–15.
42. Bhatt CP KB. SIDE EFFECTS ASSOCIATED WITH DRUGS USED IN TREATMENT OF MULTI DRUG RESISTANT TUBERCULOSIS AND TREATMENT RELATED FACTORS OF MULTI DRUG RESISTANT. *SAARC J Tuberc Lung Dis HIV/AIDS SIDE*. 2017;(1):1–6.
43. Malangu N, Adebajo OD. Knowledge and practices about multidrug-resistant tuberculosis among healthcare workers in Maseru. *Afr J Prm Heal Care Fam Med*. 2015;7(1):1–5.
44. East C and SAHC. Regional Policy on the Management of Multi-Drug Resistant and Extensively- Drug Resistant Tuberculosis Treatment Failures. 1st ed. Arusha, Tanzania: TB CARE I; 2015.
45. Yedilbayev A. DR-TB: What is new in TB treatment? In: World TB day and TRAC. Addis Ababa; 2018. p. 20.
46. World Health Organization. consolidated guidelines on tuberculosis treatment. Geneva; 2019.
47. A.J. Nunn, T. Mebrahtu, D. Meressa et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. *N Engl J Med*. 2019;380(13):1201–13.
48. Max R. O'Donnell, Allison Wolf et al. Adherence in the treatment of patients with extensively drug- resistant tuberculosis and HIV in South Africa: A prospective cohort study. *J Acquir Immune Defic Syndr*. 2015;67(1):22–9.

49. Central Statistical Agency(CSA) of ETHIOPIA. Population Projection of Ethiopia for All Regions At Wereda Level from 2014 – 2017. Addis Ababa; 2013.
50. Solomon MD, Majumdar SR. Primary Non-adherence of Medications : lifting the veil on prescription-filling behaviors. *J Gen Intern Med.* 2010;25(4):280–1.
51. Marcia A, Mendonça C, Kritski AL, Gerardin M, Land P, Couto C, et al. Abandonment of Treatment for Latent Tuberculosis Infection and Socioeconomic Factors in Children and Adolescents : Rio De. *PLoS One.* 2016;11(5):1–12.
52. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *Biomed Res Int.* 2015;15(10):1–12.
53. KENYAN MINISTRY OF HEALTH. Factors Associated With Non-Adherence to Tuberculosis Treatment in Kenya 201 8. Nairobi; 2018.
54. Mangum BP, Mangum TL, Dacanay PO et al. Review and critique of the World Health Organization ' s DOTS Programme : Recommendations to improve patient compliance in the treatment of TB and MDR TB in low-resource settings. *Vaccine Immunol Open Access J.* 2018;1(1):38–41.
55. Tupasi TE, Marie A, Garfin CG, Kurbatova E V, Mangan JM, Orillaza-chi R, et al. Factors Associated with Loss to Follow-up during Treatment for Multidrug-Resistant Tuberculosis, the Philippines, 2012–2014. *J Emerg Infect Dis.* 2016;22(3):491–502.
56. Heemanshu A, Satwanti K. Determinants of lost to follow up during treatment among tuberculosis patients in delhi. *nternational J Med Res Heal Sci.* 2016;5(1):145–52.
57. Wurie FB, Cooper V, Horne R, Hayward AC. Determinants of non-adherence to treatment for tuberculosis in high- income and middle-income settings : a systematic review protocol. 2018;1–4.
58. Amudha VP, Sucilathangam G, Jaivanth ND, Revathy C. Assessment of Risk Factors in MDR TB Patients . The Reasons behind Their Admission to DOTS plus Centres . Will They Pass Through ? *IntJCurrMicrobiolAppSci.* 2018;7(10):1775–84.
59. Lygizos M, Merwe TL Van Der, Radebe Z, Loveday M, Moll AP, Margot B, et al. Integrated, Home-based Treatment for MDR-TB and HIV in Rural South Africa: An

Alternate Model of Care. *Int J Tuberc Lung Dis*. 2013;16(8):998–1004.

60. Deshmukh RD, Dhande DJ, Sachdeva KS, Sreenivas AN, Kumar AM V. ScienceDirect Social support a key factor for adherence to multidrug- resistant tuberculosis treatment. *Indian J Rheumatol* [Internet]. 2018;65(1):41–7. Available from: <http://dx.doi.org/10.1016/j.ijtb.2017.05.003>
61. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review. *Iran J Public Health*. 2015;44(1):1–11.
62. Jakubowiak WM, Bogorodskaya EM, Borisov ES, Danilova DI, Kourbatova EK. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. *INT J TUBERC LUNG DIS*. 2007;11(1):46–53.
63. Susan van den Hof, David Collins, Ieva Leimane, Ernesto Jaramillo AG. *Lessons Learned from Best Practices in Psycho-Socio-Economic Support for Tuberculosis Patients*. Hague, Netherlands; 2014.
64. Williams AO, Makinde OA, Ojo M. Community-based management versus traditional hospitalization in treatment of drug-resistant tuberculosis : a systematic review and meta-analysis. *Glob Heal Res Policy* [Internet]. 2016;1–14. Available from: <http://dx.doi.org/10.1186/s41256-016-0010-y>
65. Schnippel K, Firnhaber C, Berhanu R, Page-shipp L, Sinanovic E. Adverse drug reactions during drug-resistant TB treatment in high HIV prevalence settings : a systematic review and meta-analysis. *J Antimicrob Chemother*. 2017;72(April):1871–9.
66. Trauer JM, Achar J, Parpieva N, Khamraev A, Denholm JT, Falzon D, et al. Modelling the effect of short-course multidrug-resistant tuberculosis treatment in Karakalpakstan , Uzbekistan. *BMC Med* [Internet]. 2016; Available from: <http://dx.doi.org/10.1186/s12916-016-0723-2>
67. Churchyard GJ. A Short Regimen for Rifampin-Resistant Tuberculosis. *N Engl J Med*. 2019;380(13):1279–80.
68. Samuels JP, Sood A, Campbell JR, Khan FA, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis : a systematic review and meta-analysis. *Sci*

Rep [Internet]. 2018;8(October):4980. Available from: <http://dx.doi.org/10.1038/s41598-018-23344-z>

69. Tola HH, Shojaeizadeh D, Garmaroudi G, Tol A, Yekaninejad MS, Ejeta LT, et al. Psychological distress and its effect on tuberculosis treatment outcomes in Ethiopia. *Glob Health Action*. 2015;8(1).
70. Ibrahim E, Ibrahim A, Aly M, Messery A. Pattern of prevalence , risk factors and treatment outcomes among Egyptian patients with multidrug resistant tuberculosis. *Egypt J Chest Dis Tuberc* [Internet]. 2017;66(3):405–11. Available from: <http://dx.doi.org/10.1016/j.ejcdt.2016.11.002>
71. Tegegne BS, Habtewold TD, Mengesha MM, Burgerhof JGM. Association between diabetes mellitus and multi-drug-resistant tuberculosis : a protocol for a systematic review and meta-analysis. *BioMed Cent* [Internet]. 2017;6(6):4–8. Available from: <http://dx.doi.org/10.1186/s13643-017-0407-9>
72. Ae Y, Yee S, Jo K, Jin H. Impact of Diabetes on Treatment Outcomes and Long-Term Survival in Multidrug-Resistant Tuberculosis. *Respir* 2013;86:472–478. 2013;86:472–8.
73. Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, et al. Risk Factors and Mortality Associated with Default from Multidrug-Resistant Tuberculosis Treatment. *Clin Microbiol Infect*. 2008;46(June):1844–51.
74. Eticha T. KE. Non-Adherence to Anti-TB Drugs and Its Predictors among TB / HIV Co-Infected Patients in Mekelle, Ethiopia. *J Bioanal Biomed*. 2014;6(6):61–4.
75. Kashongwe MI, Mbulula L, Umba P, Lepira FB, Kaswa M, Kashongwe ZM. Factors Associated with Mortality among Multidrug Resistant Tuberculosis MDR / RR-TB Patients in Democratic Republic of Congo. *J Tuberc Res*. 2017;5:276–91.

ANNEXES

ANNEX I- Information sheet and Informed Consent

Introduction: My name is _____. I am working as a data collector for the study being conducted by postgraduate student at St. Paul's Hospital Millennium Medical College department of public health.

The purpose of the study: To assess the level of non-adherence and associated factors among MDR- TB patients in SNNPR.

Duration: Your participation in the study will consist of an interview about your personal, social and clinical history and will not take more than 15 minutes

The benefit of the study: there is no direct benefit to the participant of the study but it will contribute as input in considering a convenient programmatic approach to solve the problem of non-adherence.

The risk of the study: Participating in this study will not have any risk or harm.

Rights of Participants: You have full right either to Participate or decline participation in this study as a participant. You may respond to all the questions or may not answer to questions you don't want to and you may end the interview at any time you want. You will continue to receive all medical services regardless of participation. You can ask any question which is not clear for you.

Confidentiality: Any information forwarded was kept confidential and names will not be written or specified. High levels of data security was maintained.

I have read this form or it has been read to me in the language I comprehend and understand all conditions stated above.

Are you willing to participate in this study?

1- No (say thank you)

2- Yes (continue interviewing)

Name of principal investigator: Dr. Gizaw Teka

Cell phone: 0916073420

E-mail: gizawt982 @gmail.com

- Q122. Latest Culture result 1. Positive 2. Negative 3. Unknown
- Q123. Treatment history 1. New 2. Previously treated with FLD 3. Treatment after LTFU 4. Transfer- in 5. Previously treated with SLD 6. Unknown
- Q124. Availability drugs. 1. Always available 2. Some drugs available 3. Not available
- Q125. Experience of MDRTB drugs side effects (Adverse event) 1 No. 2. Yes
- Q126. If yes, List the adverse event (AE)
1. Nausea and vomiting; 2. Hepatitis; 3. Gastritis; 4. Renal toxicity;
5. Electrolyte disturbance; 6. Optic neuritis; 7. Arthralgia, 8. Seizures;
9. Peripheral neuritis; 10. Hearing loss and vestibular disturbance, 11. Depression,
12. Psychotic symptoms, 13. Hypothyroidism 14. Others
- Q127. Grade three or more AEs 1. No 2. Yes
- Q128. Do you pay for drugs given for treating side effects of MDRTB? 1. Yes 2. No

Part IV. Client related factors

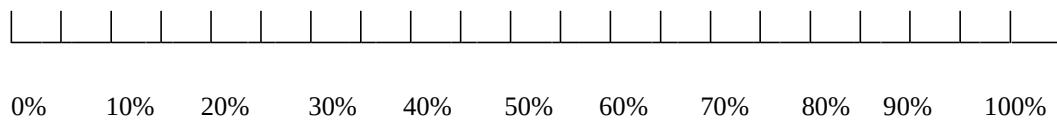
- Q129. Alcohol drinking 1. Previously used 2. Currently used 3. Never used
- Q130. Smoking cigarettes 1. Previously used 2. Currently used 3. Never used
- Q131. chewing chat 1. Previously used 2. Currently used 3. Never used
- Q132. Knowledge of MDRTB (at least three) 1. YES 2. NO
- A, Symptoms 1..... 2..... 3.....
- B, Treatment duration.....
- C, Curability 1. curable 2. Not curable 3. Don't know
- D, Transmission and Prevention methods 1..... 2..... 3.....
- Q133. HIV sero-status 1. Positive 2. Negative 3. Unknown
- Q134. Started on ART? 1. Yes 2. No
- Q135. Comorbidity other than HIV? 1. Yes 2. No
- Q136. Nutritional status (BMI) Wt.....kg; ht.....meter; BMI.....kg/m²
1. Normal 2. Mild 3. Moderate 4. Severe
- Q134. Do you ever miss taking all your anti MDRTB drugs? 1. Yes 2. No**

Q135. If yes, why? 1. Adverse events 2. Stock out of drug 3. Pill burden and fear of side effect 4. Distance of the health facility 5. Felling healthy and cured 6. Overlapping of working hour and medication time 7. Forgetfulness 8. Others

Q 136. Over the last four weeks, how often did you miss taking your anti MDRTB drugs?
1. Daily 2. More than once a week 3. Once a week 4 Once every two weeks
5. Once a month

How much of anti TB drugs have you taken as prescribed in the last three to four weeks?

VAS (Visual Analog Scale)



0% means you have taken no drugs at all

50% means you have taken half of the drugs

100% means you have taken all required pills of the drugs

ANNEX III: Amharic Version Informed consent and Questionnaire

በአማርኛ የተዘጋጀ ለተሳታፊዎች የሚነገር መረጃ እና ስምምነት ቅጽ

እኔ ስሜ _____ ይባላል። በቅዱስ ጳውሎስ ሆስፒታል ሚላንየም የህክምና ኮላጅ የህብረተሰብ ት/ት ክፍል የፊልድ ኢፒዲሚዮሎጂ ረዚደንት በሆነው በዶ/ር ግዛው ተካ ለሚሰራው ጥናት መረጃ በመስበሰብ ላይ ነኝ። የጥናቱን ሁኔታ፣ አላማና ፋይዳ ካወቁና ከተገነዘቡ በኋላ በጥናቱ ላይ ለመሳተፍ ፈቃደኛ መሆን ወይም አለመሆንዎን እንዲገልፁልኝ እጠይቅዎታለሁ።

የምርምሩ /ጥናቱ ርዕስ:- ስደት/ብ/ብ/ክ/መ ባሉ ጤና ተቆማት መድሃኒት የተላመደ ቲቢ በሽታ መድሃኒት ቢታዘዘው አግባብ መሰረት እዳንወሰድ የሚያደርጉን ምክንያቶች በተመለከተ ለማጥናት።

ዋና ዓላማውም:-መድሃኒት የተላመደ ቲቢ በሽታ መድሃኒት ቢታዘዘው አግባብ መሰረት እዳንወሰድ የሚያደርጉን ምክንያቶች በተመለከተ ለማጥናትና በጥናቱ ላይ የሚገኙት መረጃዎች ለሚመለከታቸው መስሪያ ቤቶች በማቅረብ መፍትሄ እንዲሰጣቸው ማድረግ።

ሊያጋጥም የሚችል ችግር /አለመመቻት:- መረጃ በመስጠትዎ ምክንያት የሚያጋጥምዎት ችግር የለም

ሚስጥር ስለመጠበቅ:- ለዚህ ጥናት የሚሰበሰበውን መረጃ ሚስጥር ለመጠበቅ ሲባል መረጃ የሚሰበሰበው በሰለጠኑ ባለሙያዎች እና ከሙያዉ ጋር ጥብቅ ቁርኝት ባላቸው ሰዎች ሲሆን የተሰበሰበው መረጃም ከጥናቱ ዋና ተመራማሪና ረዳቶች በስተቀር ሌላ ለማንም ሰው ግልፅ አይሆንም።

በጥናቱ አለመሳተፍ ወይም ተሳትፎን ስለማቻረጥ :- ቃለ መጠይቁ ወይም ውይይቱ የሚካሄደው በእርሶ ሙሉ ፍላጎት ላይ ብቻ ተመሥርቶ ሲሆን መመለስ የማይፈልጉአቸው ጥያቄዎች ካሉ ማለፍ ይችላሉ። ከዚህም በተጨማሪ በፈለጉበት ሰዓት ውይይቱን ማቻረጥ ይችላሉ። መሳተፍ ባይፈልጉ የህክምና ክትትል ላይ የሚያሳድረው ምንም አይነት ተጽእኖ አይኖርም።

ለበለጠ መረጃ ፡ ይህ የምርምር ፕሮጀክት ቅዱስ ጳውሎስ ሚሊኒየም ሜዲካል ኮሌጅ የሥነ- ምግባር ኮሚቴ ተልዕኮ የፀደቀ ነው። የትኛውም አይነት ጥያቄ ቢኖራችሁ ከዚህ ቀጥሎ የተጠቀሱትን ግለሰቦች ማግኘትና በማንኛውም ጊዜ መጠየቅ ይችላሉ።

ተመራማሪ፡ ዶ/ር ግዛው ተካ ስልክ ቁጥር፡ 016073420 ኢሜል፡ gizawt982@gmail.com

የስምምነት ማረጋገጫ፡ መረጃ ለመስጠት ፈቃደኛ ነዎት? 1. አዎ 2. አይደለሁም

መመሪያ፡ ቃለመጠይቁን ለማጠናቀቅ 15 ደቂቃ የሚፈጅ ሲሆን ሁሉንም ጥያቄዎች ለመመለስ ይሞክሩ። ለትእዛዝትዎ እናመሰግናለን።

- ቁ121 የቲቢ መድሃኒት የጎንዮሽ ጉዳት ነበርዎት 1. አዎ 2. አልነበረኝም
- ቁ122 መልስዎ አዎ ከሆነ የነበርዎት የጎንዮሽ ጉዳት ምን ምን ነበር (ከ1በላይ ይቻላል)
- ቁ123 መድሃኒት የተላመደ ቲቢ በሽታ የህክምና መድሃኒት ውጭ ሌላ መድኒት ይወስዳሉ 1. አዎ 2. አልወስድም
- ቁ124 መልስዎ አዎ፣ ከሆነ የምን የምን ህክምና መድሃኒት እንደሚወስዱ ይንገሩኝ
 1. የፀረ-HIV መድሃኒት 2. (CPT) 3. የኩላሊት ህመም 4. ደምግፊት (HPT) 5. ቫይረሽያል.ሲክስ
 6. አስም (Asthma) 7. የአእምሮ ህመም 8. ሰከር (DM) 9. የልብ ህመም 10. ሌላ.....
- ቁ125 መድሃኒት የተላመደ ቲቢ ህክምና ጊዜዎት ክፍያ ያላቸው መድሃኒቶች ወስደው ያወቃሉ 1. አዎ 2. አይደለም
 ክፍል አራት፡ ከደነበኛ/ታካሚ/ ጋር የተያያዙ ችግሮች
- ቁ126 የታዘዘልዎትን የቲቢ መድሃኒት አቀርጠው/ረስተው ያውቃሉ 1. አዎ 2. አይደለም
- ቁ127 ከቃለ መጠይቁ አንድ ወር በፊት ስንት ቀን ረሱ? 1. በየቀኑ 2. ከአንድ በላይ በሳምንት 3. አንድ በሳምንት 4. አንድ በሁለት በሳምንት 5. አንድ በወር
- ቁ128 የታዘዘልዎትን የቲቢ መድሃኒት አቀርጠው/ረስተው የነበረው በምን ምክንያት ነበር
 1. ረስተው/ባለማስታወስ
 2. መድሃኒቱን ስዎሰድ የጎንዮሽ ህመም ስለሚሰማኝ/ስለሚጨንቀኝ
 3. ጤና ጣቢያው ስለሚርቀኝ
 4. መድሃኒት መውሰጃውና መደበኛ ስራ ሰዓት ስለሚጋጭ
 5. በአፍ የሚዋጥ ብዙ መድሃኒታት ስለምውሰድ እና መድሃኒቱ መርዛማ ስለሆነ ጎንዮሽ ጉዳቱን ለማሰወገድ
 6. በጾም በፀበል ምክንያት
 7. ሌላ ካለ ይጥቀሱ.....
- ቁ129 መጠጥ የመጠጣት ልምድ አለዎት 1. ከቲቢ በሽታ በፊት ጠጥቶ የሚያውቅ/የምታውቅ
 2. አሁን የሚጠጣ/የምትጠጣ 3. ፍፁም ጠጥቶ/ታ የማያውቅ/የማታውቅ
- ቁ130 ሲጋራ የማጨስ ልምድ አለዎት 1. ከቲቢ በሽታ በፊት አጭሶ የሚያውቅ/የምታውቅ
 2. አሁን የሚያጨስ/የምታጨስ 3. ፍፁም አጭሶ/ሳ የማያውቅ/የማታውቅ
- ቁ131 ጫት የመጠቀም ልምድ አለዎት 1. ከቲቢ በሽታ በፊት ተጠቅሞ የሚያውቅ/የምታውቅ
 2. አሁን የሚጠቀም/የመትጠቀም 3. ፍፁም ተጠቅሞ/ማ የማያውቅ/የማታውቅ
- ቁ132 የቲቢ በሽታ በምን በምን ይተላልፋል ቢንስ ሁለቱን ጥቀሱ 1..... 2..... 3.....
- ቁ133 የቲቢ በሽታ የምንከላከልበት ዜዴ ቢያንስ አንዱን ይንገሩኝ 1..... 2..... 3.....
 የቲቢ በሽታ ህክምና ጊዜ.....
 የቲቢ በሽታ በህክምና ይድናል 1. አዎ 2. አይድንም 3. አላውቅም
- ቁ134 ስለ ቲቢ በሽታ ያላቸው አውቀት 1. ዝቅተኛ(<3) 2. በቂ(>=3)

Annex IV: Declaration form

LETTER FOR DECLARATION

I, the under signed, declared that this is my bona fide original work, has never been presented in this or any other University, and that all the resources and materials used have been fully acknowledged.

Student Name: _____

Signature: _____

Date of submission: _____

This thesis has been submitted for examination with my approval as a University advisor.

Name: Tesfaye Dagne Weldemarium (MPH) Signature _____