# ADVERSE DRUG REACTIONS AND ITS DETERMINANTS AMONG PATIENTS TREATED FOR MULTIDRUG RESISTANT TUBERCULOSIS AT ALERT HOSPITAL, ADDIS ABABA, ETHIOPIA


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JIMMA UNIVERSITY

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# ADVERSE DRUG REACTIONS AND ITS DETERMINANTS AMONG PATIENTS TREATED FOR MULTIDRUG RESISTANT TUBERCULOSIS AT ALERT HOSPITAL, ADDIS ABABA, ETHIOPIA

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# ABSTRACT

***Background:*** *Successful treatment of multidrug resistant tuberculosis requires therapy with several effective drugs some of which are highly toxic, less efficacious and expensive. Drug related adverse reactions are common causes for drug discontinuation and poor treatment outcome among patients treated for drug resistant tuberculosis. Studies related with safety of the drug and prevalence of adverse effects among patients treated for multidrug resistant tuberculosis in Ethiopia is not studied well.*

***Method:*** *Retrospective medical record review was conducted at ALERT hospital from April 21 to May 20, 2014. The study involved patient cohort who started multidrug resistant tuberculosis treatment at ALERT hospital between November 21, 2011 and October 20, 2013. The collected data was cleaned, organized and entered in to computer for analysis using SPSS version 16.0. The frequency, cross tabulation and charts are used to present the results. The mean and standard deviation was calculated for continuous variables. A P-value of less than 0.05 was considered for statistical significance.*

***Result:*** *Between November 21, 2011 and October 20, 2013 158 individuals were diagnosed with multidrug resistant tuberculosis and registered for treatment at ALERT hospital. Analysis was done for 117 patients who fulfilled the inclusion criteria. Almost all patients, 116 (99.14%) developed at least one adverse drug reaction. Hypokalemia 99 (84.6%), gastrointestinal adverse effects 70 (59.83%) and psychiatric disorders 33 (28.2%) were among the most frequently occurred adverse drug reactions. High cycloserine dose and residing at Addis Ababa were independently associated with occurrence of psychiatric disorder and treatment duration of more than 12 months was independently associated with hypothyroidism.*

***Conclusions:*** *The adverse drug reactions related with multidrug resistant tuberculosis treatment were commonly encountered among patients involved in the study. The adverse drug reactions resulted in deaths, permanent drug discontinuation and offending drug removal from drug regimen.*



***Key words:*** *Multidrug resistant tuberculosis, adverse drug reactions, second line anti tuberculosis, ALERT, Ethiopia*

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# TABLE OF CONTENTS

**PAGE**

## LIST OF TABLES

**Page**

## LIST OF FIGURE

**Page**

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse drug reactions |
| AIDS | Acquired Immuno-Deficiency Syndrome |
| ALERT | All African Leprosy and Tuberculosis Rehabilitation and Training Center |
| Cm | Capreomycin |
| Cs | Cycloserine |
| DOT | Directly Observed Therapy |
| DR-TB | Drug Resistance TB |
| DST | Drug Susceptibility Testing |
| E | Ethambutol |
| EPTB | Extra Pulmonary TB |
| ETH | Ethionamide |
| FMoH | Federal Ministry of Health |
| HAART | Highly active anti retroviral therapy |
| HBCs | High Burden Countries |
| HIV | Human Immuno-Deficiency Virus |
| MDR TB | Multi-Drug Resistant tuberculosis |
| Lfx | Levofloxacin |
| PAS | Para-amino salicylic acid |
| PTB | Pulmonary Tuberculosis |
| PZA | Pyrazinamide |
| R | Rifampicin |
| RHZE | Rifampicin/Isoniazid/Pyrazinamide/Ethambutol |
| TB | Tuberculosis |
| WHO | World Health Organization |
| XDR-TB | Extensively Drug Resistance TB |

# CHAPTER ONE: INTRODUCTION

## 1.1 BACKGROUND

Tuberculosis (TB) is a major public health problem throughout the world. About a third of the world's population is estimated to be infected with tubercle bacilli and hence at risk of developing active disease (1). There were 8.6 million incident TB cases occurred in 2012 according to the world health organization (WHO) TB report, 2013. Globally, 3.6% of new TB cases and 20.2% of previously treated cases are estimated to have multidrug resistant tuberculosis (MDR TB). The highest levels of MDR TB are found in Eastern Europe and central Asia, where in some countries more than 20% of new TB cases and more than 50% of those previously treated for TB have MDR TB. Ethiopia is one of the 27 high MDR TB burden countries. According to the 2013 WHO TB report, 1.6 % (CI 0.9-2.8) among new cases and 12% (CI, 5.6-21) among retreatment cases were estimated to have MDR TB. Based on the report 1600 (830–2700) new cases and 480 (230–870) retreatment cases were estimated to have MDR TB among notified pulmonary TB cases (2).

Multidrug resistant tuberculosis (MDR TB), defined as TB with isolates showing in vitro resistance to at least isoniazid and rifampicin, contributes to rising TB morbidity and mortality on a global level (3-5). MDR TB might be due to acquired resistance that is strain of Mycobacterium tuberculosis that was initially sensitive to Directly Observed Treatment, Short course (DOTS) drugs, but becomes resistant to drugs within an individual in the setting of low drug levels, intermittent therapy or effective monotherapy or due to primary resistance. Primary resistance is infection with a strain in Mycobacterium tuberculosis that is already resistant to important first-line drugs (6). Drug resistant TB is a man made problem, largely being the consequence of human error as a result of individual or combination of factors related to management of drug supply, patient management, prescription of chemotherapy, and patient adherence. Poor infection control practice also has been identified as a major contributing factor for the spread of MDR TB (7).

MDR TB usually does not respond to short course chemotherapy. Successful treatment of MDR TB requires therapy with several effective drugs some of which are highly toxic, less efficacious and expensive (5, 7, 8). According to the 2011 updated WHO recommendations, four second-line anti-TB drugs likely to be effective should be used. The standardized regimen should include at least

pyrazinamide, a fluoroquinolone, a parenteral agent (kanamycin, amikacin or capreomycin), ethionamide (or prothionamide), and either cycloserine or para-aminosalicylic acid (PAS) if cycloserine cannot be used. An intensive phase of 8 months' and total treatment duration of greater than or equal to 20 months is recommended in patients without any previous history of MDR TB treatment. The duration may be modified depending on bacteriological status and other indicators of progress on treatment (7, 8).

The initiatives for MDR TB treatment in Ethiopia dates back when the Green Light Committee (GLC) approved the application for cohort of 45 patients since August, 2008 and started treatment for the first group of 9 patients in February, 2009 (9). The current Ethiopian treatment strategy combines standardized and individualized treatment based on second line drug susceptibility test (DST) for all confirmed MDR TB patients. The national TB program (NTP) recommends that each MDR TB regimen should include at least four new drugs with almost certain effectiveness. As a standard all patients receive pyrazinamide, kanamycin/amikacin, levofloxacin, ethionamide and cycloserine. In case of resistance to Kanamycin/Amikacin, Capreomycin can be used as injectable and can be counted as effective drug. Ethambutol is contained if DST suggests susceptibility to the drugs. The drugs are given to all MDR-confirmed cases under daily DOTS (at least one drug intake will be medically supervised per week/ day). The injectable agent is used for a minimum of 6 months and at least 4 months after culture conversion, and total treatment is for a minimum duration of 18 months beyond culture conversion (7, 10).

Adverse drug reactions associated with second-line drugs have been mentioned as obstacles in the management of multidrug resistant tuberculosis (8, 11-13). Adverse drug reactions are "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (14). Different studies done among MDR TB treated patients had shown that the occurrence of adverse drug reactions was high (11, 12, 15-20). Among 142 patients prospectively followed between January 1995 to December 2000 in Istanbul, Turkey 55.6% (n= 79) of patients developed adverse drug reactions and the drugs commonly caused the events were cycloserine, amikacin and para-aminosalicylic acid (15). Analysis of 117 patients record for DOTS-Plus pilot project established at

Makati Medical Center in Manila, the Philippines between April 1999 and March 2002 reported that almost all patients, 96% (112 patients) experienced adverse reactions (16).

Thirty nine patients (60.9%) experienced adverse reactions among 64 patients (43 female and 21 male) who started second line TB drugs in directly observed treatment (DOT) program. The most frequently occurred drug events were gastrointestinal disturbance (51.5%), psychiatric disorders (15.6%) and dermatological effects (12.5%) (21). A retrospective analysis of seventy-six patients for early outcomes in Lesetho national MDR TB program identified that 70 patients (92%) experienced at least one serious adverse effect. The most frequently occurred adverse reactions in the study subjects were neuropathy (51%), hypokalemia (42%), ototoxicity (36%), depression (17%) and psychosis (16%) (19). Among 125 patients who received individualized therapy for MDR TB 115 patients were screened for electrolyte abnormalities and 31.3% developed hypokalemia. For patients receiving capreomycin, the incidence of hypokalemia was 68.2% (22).

## 1.2 Statements of the problems

The World Health Organization (WHO) has recognized M/XDR TB as a Major challenge to be addressed as part of the Stop TB strategy, launched in 2006 (23). In April 2009, WHO convened a ministerial meeting of countries with a high burden of MDR TB in Beijing, China, on prevention and control of MDR TB and XDR TB and urges member states to take action on multiple fronts towards achieving universal access to diagnosis and treatment of M/XDR TB by 2015 (5). Despite the important progress being made, severe challenges are limiting the response to the M/XDR TB epidemic. Among the challenges drug related adverse reactions are common and one reason for drug discontinuation and poor treatment outcomes (8, 16, 24-28). Different studies done on MDR TB treatment had shown that the occurrence of adverse drug reactions is very high, which ranges 52-96% (11, 12, 15-17, 20).

The adverse drug reactions experienced among patients treated for MDR TB are different based on the specific drug regimen used and the patient demographic and clinical conditions. In a study done at Lima (Peru) 31.3% had hypokalemia and administration of capreomycin and low initial body weight are the risk factors for this adverse reaction (22). A case-control study which was performed using information from Peru TB Program indicated that age over 40 years, overweight/obesity, anemia, MDR TB medication and smoking were independently associated with adverse drug reactions (24). Study done in Tomsk, Russia found that adverse reactions were observed in 74.8% of patients who were adherent (taking at least 80% of prescribed doses) and 59.1% of non-adherent individuals (P= 0.11) (17).

Seventy patients (28.7%) required permanent discontinuation of an offending agent due to an adverse reactions in Tomsk, Russia (17). There were 8 episodes of psychosis or severe psychiatric illness attributed to cycloserine occurred in adult XDR TB patients in KwaZulu-Natal Province, South Africa which resulted in cessation of the use of this drug. There were 4 deaths in this cohort attributed to hypokalemia or hypomagnesemia related to use of capreomycin (25). Two percent of patients stopped treatment and 30% required removal of the suspected drug(s) from the regimen due to adverse reactions among patients being treated for MDR TB at DOTS-Plus initiative sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast) (26).

Among 142 MDR TB treated patients in Istanbul, Turkey adverse effects resulted in withdrawal of responsible drugs in 35.2% (n= 50) of the patients. One patient died because of drug-induced hepatitis even after complete discontinuation of all drugs (15). From 58% of patients (67/115) who developed adverse reactions 34% (23/67) of patients required modification of treatment. The offending drug was discontinued in 28% (19/67), reactions were life-threatening in 2/67(3.0%), and 6/67(9.0%) died associated with capreomycin (hypokalaemia in 1 patient and renal failure in 5 others) (27). From adverse event experienced MDR TB treated patients in Namibia, 73% of the moderate to severe adverse reactions lasted for more than three months, while 60% of the mild adverse reactions resolved within 3 months of onset. Adverse reactions were severe and warranted discontinuation of the suspected offending medicine in four out of 26 (15%) patients (11).

Although Ethiopia developed the first national guideline for drug resistant TB and started treatment since 2009 (28) study related with second line TB drug associated adverse drug reactions were lacking. A cross sectional study conducted at St. Peter TB specialized hospital and ALERT hospital reported high prevalence of adverse drug reactions related with MDR TB treatment (29). The study used patients from two MDR TB centers on treatment between March 2012 and February 2013 but the present study was attempted to address the magnitude of adverse drug reactions and its determinants among patients treated for MDR TB at All Africa Leprosy, TB Rehabilitation and Training center (ALERT hospital), Addis Ababa, Ethiopia.

# CHAPTER TWO: LITERATURE REVIEW

## Magnitude of adverse drug reactions on patients treated for MDR TB

Treatment of MDR TB is complex and uses toxic drugs that must be administered for a longer duration than for drug-susceptible TB (7, 8, 10). Different previous studies reported that 242 (52%) in Peru (20), 79 (55.6%) in Turkey(15), 80.6% in South Africa (12), 53 (90%) in Namibia (11), 112 (96%) in Philippines study (16) and 72 (98.6%) in Ethiopia (29)experienced adverse drug reactions.

Some of these studies were cohort involving large number of patients who took treatment for MDR TB (12, 15, 20) but most of the studies were based on retrospective chart review and there could be missing of important variables from records. In addition there was no similarity in study design and sample size involved in studies which might have favored the differences in reported prevalence of adverse drug reactions (13, 16, 20).

The frequently occurred adverse drug reactions among patients treated for drug resistant TB were not uniform across studies. Gastrointestinal disturbances were commonly reported adverse reactions, 30 (45%) in Mumbai (India) (18); 34 (64%) in Namibia (11); 184 (75.4%) in Tomsk (Russia) (17) and 100% in Lima, Peru (30). Arthralgia (muscular pain) was common reported adverse effects associated with second line anti-TB drugs, 115 (47.1%) in Tomsk (Russia) (17); 36 (31%) in Philippines (16); and 15 (28%) in Namibia (11). Peripheral neuropathy is also another commonly occurred drugs side effects seen, 51% in Lesetho (19); 38% in Mumbai (India) (18); 27% in Philippines (16) and 16.7% of patients in Peru (30). Among electrolyte abnormalities associated with second line anti TB drugs hypokalemia was commonly reported, 42% in Lesetho (19); 33.2% in Tomsk (Russia) (17) and 31.3% of patients in Peru (22).

## Consequences and interventions for adverse drug reactions

Adverse reactions were the main reason for default (11/16) of patients treated for MDR TB at Philippines. The adverse reactions were managed with ancillary drugs, temporary interruption of the drug suspected (among 49% of patients) or removing the suspected drug from the treatment regimen and replacing it with a suitable alternative (16). Among patients who experienced adverse drug reactions in Tomsk, Russia capreomycin was permanently discontinued for six patients (7.4%) with hypokalemia and suspected drugs were permanently interrupted due to psychosis in 17.2% of patients who developed acute psychosis (17).

Eleven patients were hospitalized for adverse reactions and one or more suspected drugs had been permanently discontinued in 27 (40%) in Mumbai cohort. The main reasons for hospitalization were life-threatening events (severe renal impairment, hypokalaemia), seizures or severe psychiatric symptoms. Three patients died during hospitalization, eight patients were discharged recovered (18). Among 466 patients started standardized second line drugs in Peru, adverse drug reactions led permanent interruption of one or more drugs in 24 (5%) patients. An additional 61 (13%) patients underwent drug adjustments during treatment including the extension of kanamycin beyond 3 months and addition of drugs such as isoniazid, clavulanic acid, and sparfloxacin (20).

Among 91 patients (16.5%) developed hepatotoxicity in Tomsk Oblast, ten (10.9%) patients had one or more drugs permanently dropped from the regimen because of hepatitis or elevated transaminases. Other management strategies included were the use of ancillary medications and supportive care to control symptoms of side effects, such as nausea or dehydration (13). There were 8 episodes of psychosis or severe psychiatric illness attributed to cycloserine, which resulted in cessation of the use of this drug. There were 4 deaths in the cohort attributed to hypokalemia or hypomagnesemia related to use of capreomycin (25). Case records of 115 South-African XDR-TB patients were retrospectively reviewed and 161 AEs were experienced by 67/115 (58%) who started treatment. Among these patients 23 (34%) required modification of treatment, the offending drug was discontinued in 19 (28%), reactions were life-threatening in 2/67(3.0%), and 6/67(9.0%) died associated with capreomycin (hypokalaemia in 1 patient and renal failure in 5 others) (27).

## Factor associated with the occurrences of adverse drug reactions

### Patient related factors

A case-control study which was performed using information from Peru TB program indicated that age over 40 years (adjusted OR = 3.93), overweight/obesity (adjusted OR = 2.13) and smoking (adjusted OR = 2.00) were independently associated with adverse drug reactions (24). Among the nine patients (12%) who developed psychosis during treatment, younger age (average 24.1 vs. 29.7 P 0.008) was identified as a risk factor (31).

Studies conducted at Montreal Chest Institute (Montreal, Canada) among patients treated for active TB identified that occurrence of any major side effect was associated with that female sex (adjusted hazard ratio, 2.5), age over 60 years (adjusted hazard ratio, 2.9), birthplace in Asia (adjusted hazard ratio, 2.5), and human immunodeficiency virus–positive status (adjusted hazard ratio, 3.8) (32). Among patients treated for MDR TB low initial body weight was identified as risk factors for hypokalemia (22). Weight loss during active TB treatment and age over 60 years are the most important risk factor for drug induced hepatotoxicity necessitating interruption of anti-TB drugs (33).

### Disease related factors

The higher incidence of adverse reactions was seen in MDR TB patients co-infected with HIV/AIDS with regard to peripheral neuropathy (p-value < 0.001), psychosis and confusion (p-value = 0.04), hearing loss and vestibular disturbances (p-value = 0.047), and thyroid disease (p-value < 0.001) (12). Anemia was found to be independently associated with TB drugs adverse effects in one study (24). Baseline elevated alanine aminotransferase/aspartate aminotransferase/ bilirubin and renal insufficiency for patients on MDR TB treatment are risk factors for hepatotoxicity (13).

**Drug related factors**

MDR TB medication use (adjusted OR = 11.1) was independently associated with adverse drug reactions (24). Capreomycin, which was empirically administered in most of South African XDR TB patients was withdrawn in 14% (14) patients, implicated in 41% (14/34) of the total drug withdrawals, and was associated with all 6 deaths (renal failure in five patients and hypokalemia in one patient) (27). Administration of capreomycin was independently associated with the occurrence of hypokalemia (22).

Among patients being treated with first line anti-tuberculosis drugs pyrazinamide related adverse reactions were associated with age over 60 years (adjusted hazard ratio, 2.6) and birthplace in Asia (adjusted hazard ratio, 3.4) (32). The co-administration of para-aminosalicylic acid (PAS) with ethionamide was found to double the risk of hypothyroidism (34). Patients on MDR TB treatment who were taking efavirenz (EFV) containing regimens accounted for 60% (3 cases) of seizures and 92.3% (12 cases) of psychoses or confusion (12).

## 2.2 Conceptual Frame Work

MDR TB treatment is a great challenge to the world in general and to the high burden countries (HBCs) in particular because it has multi factorial issues which affects its outcome. ADRs of the treatment regimen is one among which can modify patient outcome in different ways. There are different factors that can determine the occurrence of ADRs to the patients taking MDR TB treatment. Patient characteristics, disease condition and drug related factors are some of the conditions to be closely followed in these patients.

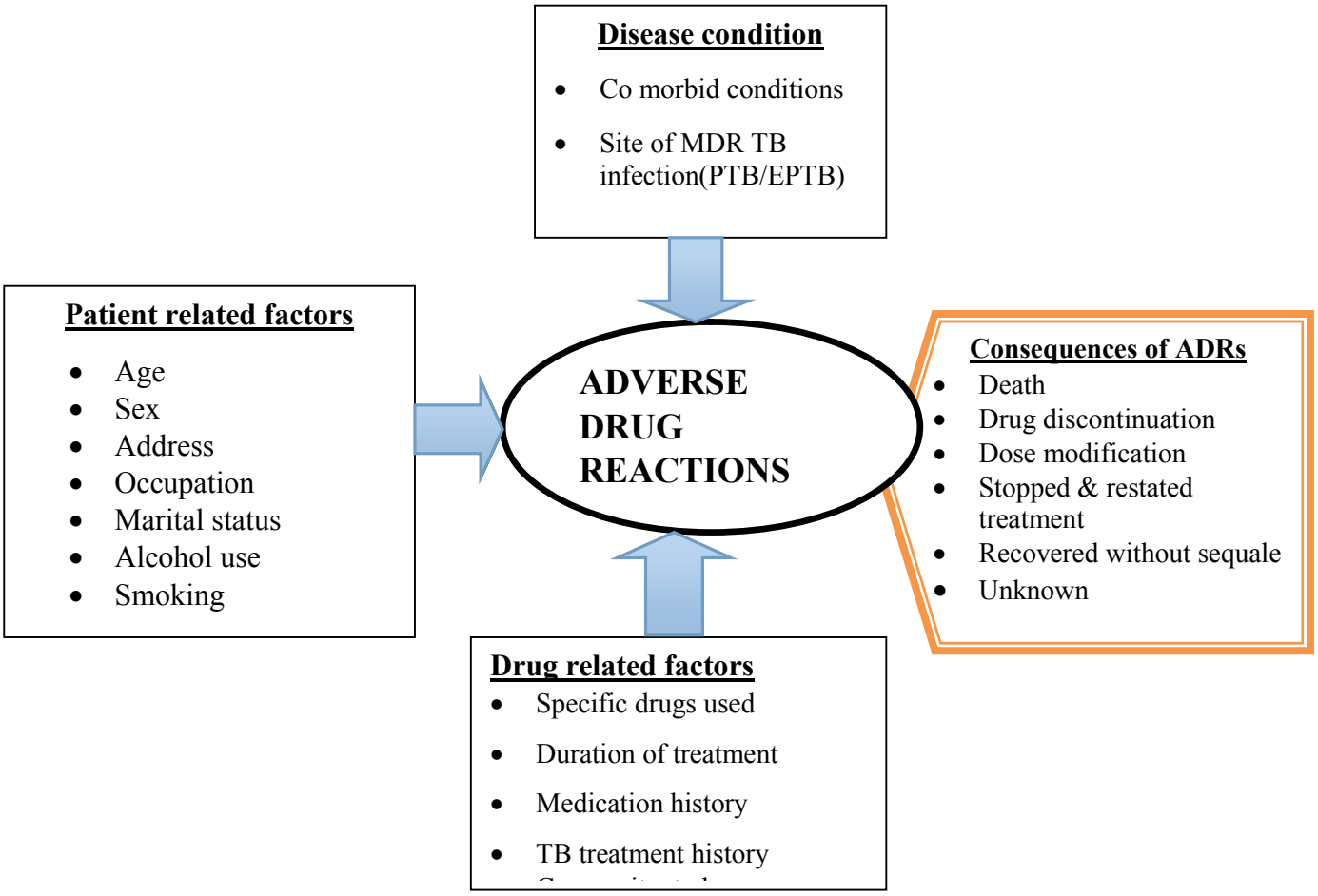


**Figure 1**: conceptual frame work showing the adverse drug reactions and the associated factors of patients treated for MDR TB at ALERT hospital April, 2014

## 2.3 Significance of the study

Studies related with safety of the drug, risk factors associated and prevalence of adverse drug reactions among patients treated for MDR TB in Ethiopia is not studied well. Because of the limited studies done to know the magnitude of the problem and the consequences on patients, conduction of this study was aimed to provide scientifically sound findings on adverse drug reactions and the determinant factors among MDR TB treated patients at ALERT hospital.

The findings of the study might have advantages to the hospital in planning and implementing issues related with ADRs to ensure patients safety which could minimize the cost incurred due to hospital stay and treating the ADRs.

MDR TB service providing health institutions, government body and other stakeholders could use the findings in reducing cost of treatment and poor treatment outcomes by preventing and early management of ADRs.

Academicians and researchers can use the findings as a base line for further studies in the area of MDR TB. Generally, understanding the prevalence of ADRs and the determinant factors have positive impact on designing effective prevention and management of second line MDR TB drug related ADRs.

# CHAPTER THREE: OBJECTIVES

## 3.1 General objectives

- To determine adverse drug reactions and the determinants among patients treated for multidrug resistant tuberculosis at ALERT hospital, Ethiopia

## 3.2 Specific objectives

- To determine the prevalence of adverse drug reactions among patients taking treatment for MDR TB
- To determine the consequences of adverse drug reactions among patients developed ADRs
- To identify the determinants for the major adverse drug reaction occurrence among patients treated for MDR TB
- To assess the interventions considered for patients experienced adverse drug reactions

## 3.3 Research questions

- What is the prevalence of ADRs among patients on treatment for MDR TB at ALERT hospital
- What are the consequences associated with ADRs to patients on treatment for MDR TB at ALERT hospital
- What are the determinants for the occurrence of ADRs to patients on treatment for MDR TB at ALERT hospital
- What are the interventions being considered for management of ADRs occurred to patients on treatment for MDR TB at ALERT hospital

# CHAPTER FOUR: METHODS AND PATIENTS

## 4.1 Study area and period

The study was conducted at All Africa Leprosy, TB rehabilitation and training center (ALERT hospital), which is located in Kolfe Keranio Kifle Ketema, Addis Ababa and it is one of the research center. The data was collected in the period of April 21 to May 20, 2014. The MDR TB service started in the hospital for patients referred from different part of the country and from central Addis Ababa since November 2011. The MDR center has total of 30 beds and it has counseling and monitoring facilities as well as surgical ward.

## 4.2 Study design

Retrospective general cohort

## 4.3 Population

### 4.3.1 Source population

All MDR TB patients registered for MDR TB treatment at ALERT hospital

### 4.3.2 Study population

Patients who were treated for MDR TB in the period of November 2011 to October 2013

### 4.3.3 Study unit

MDR TB patient who was on treatment or finished the treatment period

## 4.4 Eligibility criteria

### 4.4.1 Inclusion criteria

Patients were included in the study if the following criteria fulfilled

- Documented MDR TB
- Completed MDR TB treatment or on treatment for a month

### 4.4.2 Exclusion criteria

Patients with the following criteria were excluded from analysis in this study.

- Eleven patients with missing of treatment data like drug regimen the patient was taking, patient demographic information (identification, gender, weight, age) or incomplete records of patients treatment data
- Thirty patients were on trial of new drug regimen and the data were not allowed for the study

## 4.5 Sample size and Sampling techniques

All patients being treated or on treatment for MDR TB from November 2011 to October 2013 were included in the study.

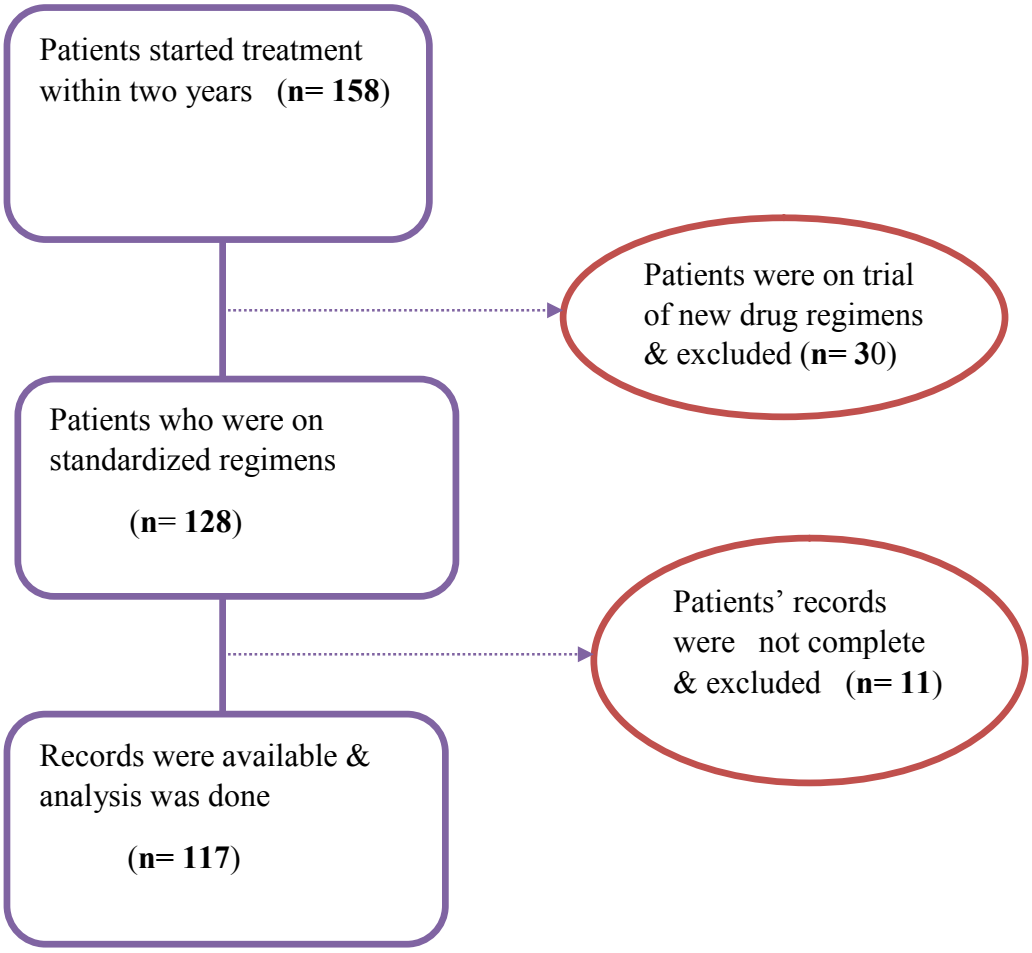


***Figure 2:*** *Flow chart showing the number of patients involved in the study from ALERT center, Ethiopia, April 2014*

## 4.6 Study Variables

### 4.6.1 Independent variables

Patient related factors

- Age
- Sex
- Address
- Weight
- Educational level
- Marital status
- Alcohol use
- Smoking status

Disease related factors

- Site of MDR TB infection (PTB or EPTB)
- Co morbid conditions

Drug related factors

- Specific second line drugs used
- Duration of treatment
- Concomitant drug use

### 4.6.2 Dependent/outcome variables

Major adverse drug reaction (Psychiatric disorder, peripheral neuropathy & hypothyroidism)

## 4.7 Data collection

### 4.7.1 Data collection instruments

Data was abstracted from MDR TB patients follow up records and medication cards using semi-structured data abstraction format. The contents of format was drug therapy part, relevant laboratory values, socio-demographic data and other clinical findings related with MDR TB treatment.

### 4.7.2 Data collection process

Data was collected from MDR TB patients follow up records and medication card by the data collectors under close follow up by principal investigator. The laboratory data like serum potassium, creatinine, thyroid stimulating hormone (TSH) and the liver function tests (ALT/AST) were monitored monthly or weekly whenever frequent follow up required. Clinical parameters which were suspected to be related with the MDR TB drugs were recorded by physician as adverse drug reaction while the patients were admitted for intensive phase in the hospital and at every follow up.

Three degree holder nurses were trained on data abstraction and chart review for two days and accordingly the data was collected.

### 4.8 Data processing and analysis

The collected data was edited, cleaned, and fed into a computer using SPSS version 16.0 for analysis. The computer fed data cross checked with the original data to ensure accuracy of entry. Descriptive statistics used to show results in the frequency tables, figures, means and percentages. Cross tabulations used for comparison of categorical variables with outcome variable. Variables with p-value of less than 0.25 in binary logistic regression are entered into multiple logistic regressions to see variables independently associated with the outcome variable. A p-value of less than 0.05 was considered for statistical significance. Microsoft Excel was used to draw chart.

### 4.9 Case detection method used

Patients follow up records (cards) and treatment cards were used to collect socio-demographic, clinical monitoring parameters, drug regimen used, the adverse drug reactions occurred and management approaches used. The treatment related adverse drug reactions collected by data collectors from medication cards were further checked by principal investigator and the unrecorded ADRs were taken from patients follow up records. The clinical and laboratory monitoring records were defined or interpreted as the treating physicians /clinicians documented as it was related with MDR TB drugs.

### 4.10 Data quality assurance

Pre-test of data abstraction format was done at Shenen Gibe hospital found at Jimma town. The data was collected by three trained nurses. The daily collected data was strictly checked for the quality and completeness by principal investigator.

### 4.11 Ethical considerations

Letter of ethical clearance was obtained from Jimma University Research Ethics Committee. The patient data was accessed after Armauer Hansen research Institute/ALERT ethical review committee approved the study proposal. Information that was taken from patients medical records are used only to identify adverse drug reactions associated with MDR TB treatment. The data collection process was carefully guided by the investigator and data collectors were trained on data collection process,

handling the patient data confidentiality and appropriate data abstraction as per the data collection tool only. The name of individual patient was not included in data collection tool instead the unique code was given for each patient medical card to ensure confidentiality.

## 4.12 Data dissemination

The findings of the study was compiled and organized to be presented to Jimma University, college of public health and medical science, to professional associations and other regional and federal government bodies of Ethiopia. Efforts will be done to publish the findings either at local or international health related journals.

## 4.13 Definitions of terms and operational definitions

**Multidrug resistant TB (MDR TB)** is caused by bacteria that are resistant to at least ionized and rifampicin, the most effective anti TB drugs (35)

**Extensively drug resistant TB (XDR-TB)** is a form of TB caused by bacteria that are resistant to ionized and rifampicin (i.e. MDR TB) as well as any fluoroquinolone and any of the second line anti-TB injectable agents (amikacin, kanamycin and/or capreomycin) (35).

**Green light committee (GLC**) is a subgroup of the MDR TB Working Group of the Stop TB Partnership, and an advisory body of WHO that promotes access to (and monitors the use of) quality-assured, life-saving MDR TB treatment (23)

**Adverse drug reaction (ADR):** Any unexpected and inappropriate medical occurrences in a patient or subject administered a pharmaceutical product and which does not necessarily have a causal relation to the treatment (14). An ADRs can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding) symptom, or disease temporarily associated with the use of a drug product.

**Pulmonary M(X) DR-TB:** refers to disease involving the lung parenchyma (7)

**Extra-pulmonary M(X) DR-TB:** refers to organs other than the lungs. A patient with both pulmonary and extra-pulmonary M(X) DR-TB constitutes a case of pulmonary M(X) DR-TB.

**Standardized treatment:** Drug Resistance Survey (DRS) data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen (7, 35).

**Individualized Treatment**: Each regimen is adopted according to guidelines based on the patient's past history of TB treatment, individual FL- and SL-DST results and possible side-effects (7, 35).

**Empiric Treatment:** Each regimen is individually designed based on the patient's past history of TB treatment and with consideration of DRS data from the representative patient population. An empirical regimen is adjusted when DST on individual patient becomes available (7).

**Category I:** It includes those new patients who have smear-positive Pulmonary TB and those who are seriously ill patients with smear-negative Pulmonary and Extra-pulmonary TB. The treatment regimen for this category is 2 (RHZE)/ 6 (EH) or 2 (RHZE) / 4RH (36)

**Category II:** This category is applied to a group of TB patients, who relapsed after being treated and declared free from the disease, or in those patients who are previously treated for more than one month with short course chemotherapy or long course chemotherapy , and found to be smear positive upon return, or who still remain smear positive while under treatment at month five and beyond. The treatment regimen for this category is: 2 SE (RHZ) / 1E (RHZ) / 5 E3 (RH)3 (36)

**Category III:** This refers to patients who have smear negative Pulmonary TB, Extra-pulmonary TB and TB in Children. The regimen consists of 8 weeks of treatment with, Ethambutol, Rifampicin, Isoniazid and Pyrazinamide during the intensive phase followed by Ethambutol and Isoniazid six months [2(RHZE)/6(EH)] (36)

**Treatment outcome definitions used in this study (37)**

**Cured:** Treatment completed as recommended by the national policy 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 as recommended by the national policy 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.

**Died:** patient died for any reason during the course of treatment.

**Lost to follow-up:** A patient whose treatment was interrupted for two consecutive months or more.

**Not evaluated:** A patient for whom no treatment outcome is assigned (this includes cases 'transferred out' to another treatment unit and whose treatment outcome is unknown).

**Definitions used for adverse drug reactions (ADRs):**

**Hypokalemia:** At least one serum potassium value of <3.5 mmol/l (38)

**Gastrointestinal adverse effects:** The presence of clinical signs and/or symptoms presented as one or more of the following; Nausea and vomiting, diarrhea, gastritis, dyspepsia and abdominal pain

**Psychiatric disorders:** Presence of one or more of the following: acute psychosis, depression and insomnia as evaluated by psychiatrist

**Arthralgia:** Pain of the joints as reported by patient and documented by physician, with or without the presence of arthritis

**Peripheral neuropathy:** Symptoms and findings consistent with neuropathy, as diagnosed by physician

**Hypothyroidism:** A thyroid stimulating hormone (TSH) result >10 mIU/L at least once during treatment (39)

**Dermatological effects:** Clinical signs/symptoms which includes skin rash, itching, acne vulgaris and psoriasis versicolar

**Renal toxicity:** Serum creatinine >1.2 mg/dl(male) or > 0.9 mg/dl (female) (39)

**Ophthalmologic effects:** Presence of one or more of the following clinical sign/symptoms as diagnosed by ophthalmologist; optic neuritis, photophobia and allergic conjunctivitis

**Hepatotoxicity:** Elevation of liver enzymes (ALT or AST) by three times the upper normal bound with Clinical signs/symptoms of hepatitis like right upper quadrant pain, jaundice, nausea or vomiting (38)

# CHAPTER FIVE: RESULTS

## 5.1 Sociodemograghic characteristics of patients

The patients' treatment records were available and analysis was done for 117 patients. Sixty eight (58.1%) patients were male. Majority of the patients were within 21-35 years age group and the mean age was 29.03 ±11.08 (range, 2 to 69 years). Seventy two (61.5%) patients were from Addis Ababa and most of patients, 74 (63.2%) weight above 45 kilogram. Sixty seven patients (57.3%) were single and 44 (37.6%) were married and most of the individuals were unemployed 83 (70.94%). Most of patients, 107 (91.5%) were educated. (Table 1)

**Table 1**: Sociodemograghic characteristics of patients treated for multi drug resistant tuberculosis at ALERT Hospital, Ethiopia, April 2014 (n= 117)

| **Variables** | **Categories** | **Number (%)** |
|---|---|---|
| Sex | Male | 68(58.1) |
| | Female | 49 (41.9) |
| Age ( yrs) | 2-20 | 25 (21.4) |
| | 21-35 | 68 (58.1) |
| | ≥36 | 24( 20.5) |
| Weight (kg) | 7-45 | 43 (36.8) |
| | ≥46 | 74(63.2) |
| Address | Addis Ababa | 72 (61.54) |
| | Out of A.A | 45 (38.46) |
| Occupation | Employed | 34 ( 29.06) |
| | Unemployed | 83 (70.94 ) |
| Educational status | Illiterate | 8 (6.8) |
| | Literate * | 107 (91.5) |
| | Pre-school age | 2 (1.7) |
| Marital status | Single | 67 (57.3) |
| | Married | 44 ( 37.6) |
| | Divorced | 6 (5.1) |

*Literate (educated) mean for individuals educated primary level and above

### 5.2 TB treatment and clinical characteristics of patients treated for MDR TB

The past TB treatment history of individual patient indicates that 110 (94.02%) patients were treated for drug susceptible TB and seven patients (5.98%) were not treated for TB before. Those individuals with previous TB treatment history 90 patients (90.9%) were treated with category I or category II or both. One hundred one (86.3%) of the MDR cases were pulmonary and the others were extra pulmonary. Regarding alcohol use and smoking habit more than 90% were non smoker and alcohol user. Twenty eight (23.9%) patients had Comorbid diseases and HIV/AIDS was the highest Comorbid disease condition, 16 (13.67%) and majority of patients with HIV co morbidity used Efavirenz based ARV drug regimen compared with protease inhibitor based (14 versus 2). The treatment outcome was known for 30 patients (27.35%) at the time of data collection. (Table 2)

***Table 2:*** TB treatment and clinical characteristics of patients treated for Multi Drug Resistant Tuberculosis at ALERT hospital, Addis Ababa, Ethiopia, April, 2014 (n= 117)

| Clinical parameters | Category | Number (%) |
|---|---|---|
| Previous TB treatment history | Yes | 110 (94.02) |
| | No | 7 (5.98) |
| Previous TB treatment regimens | Category I | 29 (26.36) |
| | Category II | 21(19.1) |
| | Category I & II | 50 (45.45) |
| | Unknown | 10 (9.09) |
| Site of MDR TB | Pulmonary | 101 (86.3) |
| | Extra pulmonary | 16 (13.7) |
| Alcohol user | Yes | 10 (8.5) |
| | No | 107 (91.5) |
| Smoking status | Yes | 6 (5.12) |
| | No | 111(94.88) |
| Comorbid conditions | HIV/AIDS | 16 (13.7) |
| | Diabetes mellitus | 3 (2.56) |
| | Others* | 9 (7.69) |
| ARV drugs used | Efavirenz based regimen | 14 (87.5 ) |
| | PI based regimen | 2 (12.5) |
| Treatment outcomes | Cured | 12 (10.25) |
| | Complete | 10 (8.54) |
| | Default | 5 (4.3) |
| | Died | 3 (2.56) |
| | Not evaluated | 87 (74.35) |

*Comorbid diseases like heart disease, lung abscess, hypertension, deep vein thrombosis, and anemia PI = protease inhibitors

### 5.3 Standardized MDR TB drug regimens used in the study patients

One hundred fourteen (97.4%) patients used the combination of drugs containing Pyrazinamide, Capreomycin, Levofloxacin, Ethionamide and Cycloserine for treatment of MDR TB. Capreomycin was the only injectable drugs used during intensive phase by all study individuals. Ethambutol considered as part of MDR regimen for 66 (56.41%) study individuals. The total number of MDR TB drugs used in the intensive phase per patient ranges from 5 to 6. Ninety (76.9%) MDR TB cases were resistant for rifampicin and isoniazid while the others were resistant for one or two first line drug in addition to rifampicin and isoniazid. During the time of study period the average duration of treatment was 14.79 ± 6.28 months (mean ± standard deviation) and the average duration of injectable drug use was 8.72 ± 1.92 months (range 4–16 months).

***Table 3****:* Standardized drug regimen used for treatment of Multidrug resistant tuberculosis at ALERT Hospital, Ethiopia, April 2014 (n= 117)

| | MDR drug regimen used | | Number (%) |
|---|---|---|---|
| Intensive phase | PZA + Cm + Lfx + ETH + Cs | | 50 (42.7) |
| | PZA + Cm + E + Lfx + ETH + Cs | | 64 (54.7) |
| | PZA + Cm + Lfx + ETH + PAS | | 1 (.9) |
| | PZA + Cm +E + Mfx + ETH + Cs | | 2 (1.7) |
| *Continuation phase* | PZA + Lfx + ETH + Cs | | 42 ( 35.89) |
| | PZA + E + Lfx + ETH + Cs | | 38 (32.47) |
| | PZA + Lfx + ETH + PAS | | 2 ( 1.7) |
| | PZA + Mfx + ETH + Cs + E | | 2 ( 1.7) |
| | Unknown# | | 33 ( 28.2) |
| Daily MDR | Pyrazinamide | 200-1750 | 74(63.24) |
| | | 2000-2500 | 43 (36.76) |
| drug dose ( mg) | Ethambutol | <1000 | 2(3.03) |
| | | 1200 | 39 (59.1) |
| | | 1600-1800 | 25 (37.87) |
| | Capreomycin | <500 | 2 (1.71) |
| | | 500-750 | 71 (60.68) |
| | | 765-1000 | 44 (37.6) |
| | Cycloserine | 250-500 | 36 (30.76) |
| | | 750-1000 | 81(69.24) |
| | Levofloxacin | 750-1000 | 115 (98.3) |
| | Ethionamide | 250-500 | 36 (30.76) |
| | | 750-1000 | 81 (69.24) |

**Continued from table 3 …**

| | | |
|---|---|---|
| | Moxifloxacin 100-200 | 2 (1.7) |
| | PAS 8000 | 2 (1.7) |
| Duration of treatment (months) | Intensive phase | 8.72 (± 1.92) |
| | Total treatment | 14.79 (± 6.28) |
| Spectrum of drug resistance | RH | 90 (76.9) |
| | RHS | 9 (7.7) |
| | RHE | 5 (4.3) |
| | RHSE | 13 (11.1) |

RH = Rifampin & Isoniazide RHS = Rifampin, Isoniazide & Streptomycin RHE = Rifampin, Isoniazide & Ethambutol RHSE = Rifampin, Isoniazide, Streptomycin & Ethambutol

The duration of MDR TB treatment was calculated as mean ± standard deviation in months

#The patient was not completed intensive phase and the drug regimen of continuous phase not known

### 5.4 Magnitude of adverse drug reactions

In this study almost all patients, 116 (99.14%) developed at least one adverse drug reaction. Three hundred seventeen (317) adverse events with the average number of 2.73 ± 1.247 (mean ± standard deviation) per patient was occurred (Figure 2 below). The most frequently occurred ADRs in the current study were hypokalemia 99 (84.6%), gastrointestinal adverse effects 70 (59.83%), psychiatric disorders 33 (28.2%), Arthralgia 31 (26.5%), peripheral neuropathy 25 (21.4%), and hypothyroidism 21 (17.95%).

Three patients (2.56%) developed complications secondary to ADRs ( one patient experienced upper GI bleeding secondary to severe gastritis and two patients developed hypokalemic tetany and/or tachyarrhythmia which were secondary to hypokalemia). For the patients with complication symptomatic management was done with administration of propranolol 40 mg tablet (arrhythmia), cimetidine 200 mg IV (upper GI bleeding) and potassium chloride tablet or IV and calcium gluconate 10% IV used for patients developed hypokalemic tetany.

Potassium chloride tablet was prescribed for 96 patients (82.1%) who developed hypokalemia. Omeprazole and cimetidine tablets or IV were commonly prescribed drugs for patients who developed gastrointestinal disorder. Haloperidol, Chlorpromazine and Amitryptyline were drugs used for management of psychiatric disorders (acute psychosis, insomnia and depression) respectively.

***Table 4**:* Adverse drug reactions and management approach used for MDR TB patients at ALERT hospital, Addis Ababa, Ethiopia April, 2014 (n=116)

| Adverse drug reactions | Number (%) | Suspected drug/s | Symptomatic managements used |
|---|---|---|---|
| Hypokalemia | 99 (84.6) | Cm | Potassium chloride 600 mg tablet or KCL IV supplemented<br>Hypokalemia defined as **mild** when serum $K^+$ is 3.1 -3.4 ; **moderate** as $K^+$ level is between 2.5-3.0 and **severe** when serum $K^+$ is $\leq$ 2.4 mmol/dl |
| Gastrointestinal adverse effects | 70 (59.83) | ETH & PAS | Antiemetic agent (metoclopramide 10 mg po/im for 33 (28.2%) patients)<br>Omeprazole 20 mg for 68 (58.11%) patient and cimetidine 200-400 mg po/IV 18 (15.4%) |
| Psychiatric disorder | 33 (28.2) | Cs | Haloperidol 2.5-5 mg tablet for six (5.1%) patients , chlorpromazine 50-100 mg po/IV for 20 (17.1%) patients, diazepam 5-10 mg po/iv used in 17 ( 14.5%), Amitryptiline 25-50 mg 8 (6.84%) and flouxetine 20 mg 2 (1.7%) patients |
| Arthralgia | 31 (26.5) | PZA, Lfx, ETH, E & Cs | Indomethacine / diclofenac suppository 100 mg for 43(36.8%) patients<br>Tramadol injection and predinsolone for two patients |
| Peripheral neuropathy | 25 (21.4) | Cs & ETH | Pyridoxine 100-200 mg given for 68 (58.11%) patients as prevention<br>Amitryptiline 25-50 mg given to 5 (4.3%) patients |
| Hypothyroidism | 21(17.95) | ETH | Thyroxin 50-100 microgram 20(17.1%) patients |
| Dermatological effects | 7 (5.98) | PZA | Salicylic acid and sulfur ointment 3 (2.6%), citirzine tablets and visiline |
| Renal toxicity | 6 (5.1) | Cm | Dose reduction of suspected drugs (capreomycin) and temporary withholding of suspected or all drugs |

| | | | |
|---|---|---|---|
| Ophthalmologic effects | 4 (3.42) | E | Ciprofloxacin eye drop<br>Chlorpheniramine tablet<br>Withdrawal of offending agent (Ethambutol) |
| Hepatotoxicity | 3 (2.6) | PZA & ETH | Dose reduction and discontinuation of suspected drug and all drugs discontinued in one patient |
| Others* | 6 ( 5.12) | | Codeine phosphate tablet, xylomethazoline nasal drop and heamup ® syrup |

* chest pain 3(2.6%), allergic rhinitis 2(1.7%), Anemia 1(0.9%) Cm = capreomycin Cs = cycloserine PZA = pyrazinamide E = Ethambutol ETH = ethionamide Lfx = Levofloxacin PAS = Para-amino salicylic acid

The maximum number of ADRs per patient experienced was six and minimum of one. Fifty eight patients (49.6%) developed three and above ADRs and 42 (35.9%) patients developed two ADRs while 16 (13.7%) patients developed a single ADR. The patients in the age group of 21-35 years experienced highest number of ADRs, 184 (58.04%) occurred compared with other two age groups.

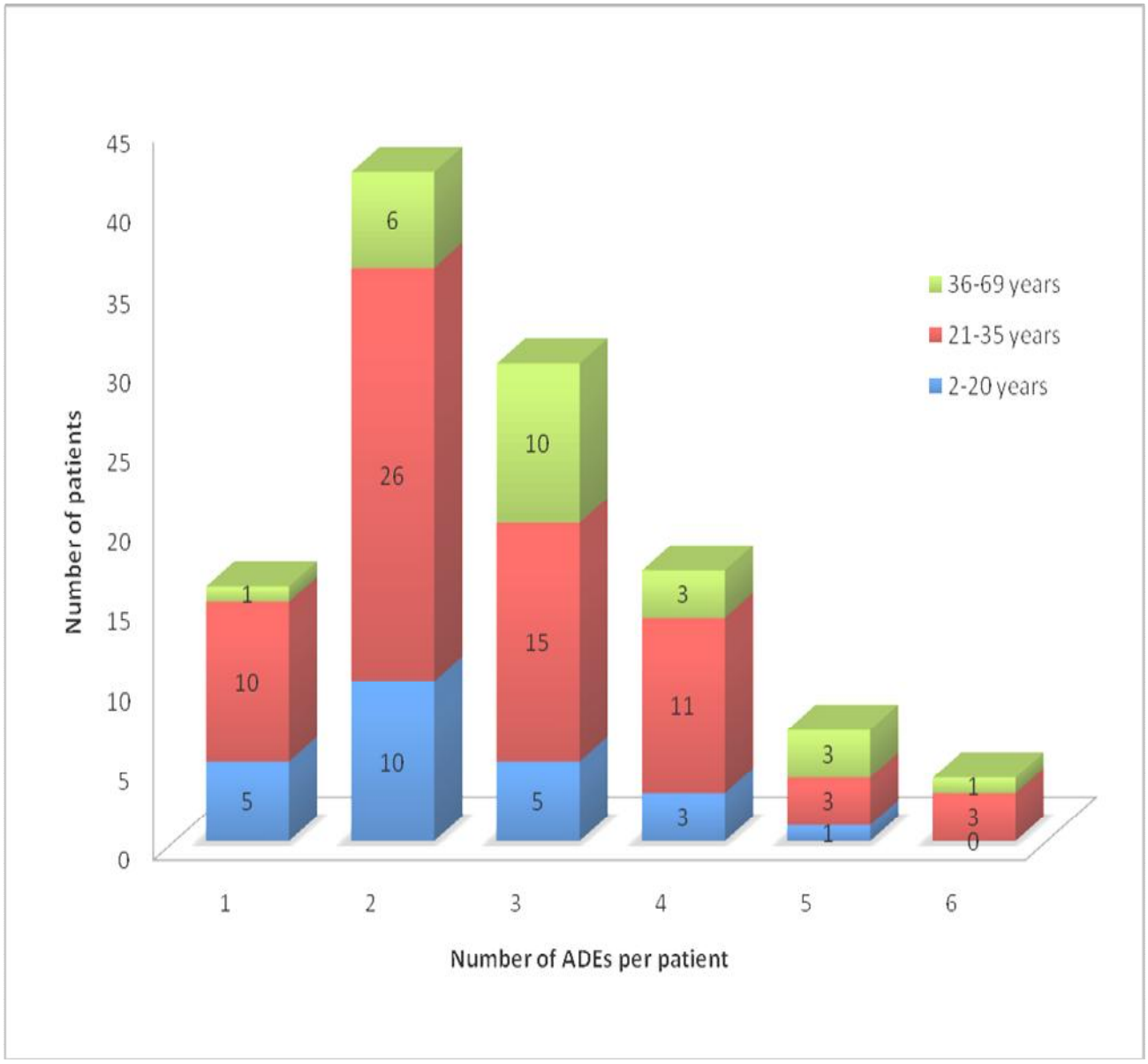


***Figure 2:*** *The number of patients experienced ADRs versus number of ADRs developed per patient treated for MDRTB at ALERT hospital, Addis Ababa, Ethiopia April 2014(n=116)*

### 5.5 Interventions and the consequences of ADRs for patients on MDR TB treatment

The adverse drug reactions caused suspension of suspected drugs for 19 patients (16.37%) and all MDR regimens suspended for 8 patients (6.89%). Dose reduction of suspected drug was done for 13 patients (11.2%) and permanent discontinuation of one drug for 4 patients (3.44%). Of those patients three patients developed recurrent psychosis and Cycloserine changed to Para-amino salicylic acid (PAS) and one patient developed severe gastritis and PAS changed to Cycloserine.

Sixty eight patients (58.62%) who developed ADRs were resolved without any permanent disability. The consequence of adverse reactions was not known for 44 patients (37.93%). Two patients died related with the drug reaction (1.72%). Two patients permanently discontinued all MDR drugs (1.72%).

**Table 5**: The interventions and consequences of ADR developed patients who were treated for MDR TB at ALERT Hospital, Addis Ababa, Ethiopia April, 2014 (n=116)

| | **Categories** | **Number (%)** |
|---|---|---|
| **Interventions to ADRs** | Suspension of suspected drug/s | 19 (16.37) |
| | Suspension of all drugs | 8 ( 6.89) |
| | Permanent discontinuation of suspected drug | 4 (3.44) |
| | Dose reduction of suspected drug/s | 13 (11.2) |
| | Increased laboratory monitoring | 116 (100) |
| **Consequences of ADRs** | Resolved without any permanent sequale | 68(58.62) |
| | Unknown* | 44(37.93) |
| | Died | 2 (1.72) |
| | Permanent discontinuation of treatment | 2 (1.72) |

*The effects of ADR was not recorded or the patients were appointed for monthly monitoring or not on follow up at the time of chart review

### 5.6 Common adverse drug reactions and MDR TB drug dose reduction or suspension

For twenty seven patients (23.27%) daily drug dose was interrupted because of different adverse drug reactions. Seventy five daily drug dose of all second line drugs were discontinued for eight patients (6.89%). One hundred thirty daily dose of capreomycin was discontinued in 10 patients (8.62%). Cycloserine discontinued in 8 patients on average for about 16.88 days. PAS was discontinued on two patients for two weeks on average (14 ± 12.72). Hypokalemia caused dose reduction of Capreomycin in 8 patients. Acute psychosis resulted in suspension of Cycloserine on 6 patients. Hypokalemia, severe gastritis, acute psychosis and hepatotoxicity were the life threatening adverse drug reactions that caused suspension of all MDR drug regimens.

**Table 6:** Common adverse drug reactions and dose reduction and/or drug interruption of second line TB drugs used for treatment of multidrug resistant TB in ALERT Hospital, Addis Ababa, Ethiopia April, 2014 (n= 116)

| | **Categories** | **Number of patients (%)** | **Average day Drug discontinued (mean ± stand. Dev)** | **Sum (minimum, maximum) of days drug interrupted** |
|---|---|---|---|---|
| ***Any drug suspended*** | Yes | 27 ( 23.27) | - | - |
| | No | 89 (76.73) | - | - |
| ***Suspected or all drug regimen discontinued*** | Z+ Cm + Lfx + ETH +Cs | 3 (2.56) | 17 (±19.46) | 51 (2,39) |
| | Z+ Cm+ E+ Lfx + ETH +Cs | 4 (3.41) | 4.25 (±2.63) | 17 (2,8) |
| | Z+ Cm + Lfx + ETH + PAS | 1 (0.85) | 7(±0.00) | 7 |
| | Cycloserine | 8 (6.84) | 16.88 (±11.21) | 135 (5,42) |
| | Capreomycin | 10 (8.54) | 13 (±4.98 ) | 130 (4,17) |
| | PAS | 2 (1.7) | 14 (± 12.72 ) | 28 (5,23) |
| ***ADRs occurred*** | *Drug caused ADRs* | *Dose reduction ( n= 13)* | Suspension *of a drug ( n= 19)* | Suspension *of all drug ( n= 8)* |
| *Hypokalemia* | Capreomycin | 8 (61.5%) | 7 (36.84%) | 1 (12.5%) |
| *Acute psychosis* | Cycloserine | 2 (15.4%) | 6 (31.6%) | 2 (25%) |
| *Severe gastritis* | *PAS | 1 (7.7%) | 1 (5.26%) | 4 (50%) |

| | | | | |
|---|---|---|---|---|
| *Renal toxicity* | Capreomycin | 1 (7.7%) | 2 (10.52%) | - |
| *Hepatotoxicity* | Pyrazinamide | - | 1 (5.26%) | 1 (12.5%) |
| *Psychosis and severe gastritis* | Cycloserine & PAS | 1 (7.7%) | 1 (5.26%) | - |
| *Psychosis and Hypokalemia* | Cycloserine & Capreomycin | - | 1 (5.26%) | - |

*PAS caused severe gastritis in one patient and the drug/s which caused severe gastritis in three patients is unknown but all drug discontinued in all cases

### 5.7 Bivariate analysis of drug related and sociodemograghic factors related with adverse drug events

Among the different drug related factors dose of drugs (Cycloserine, Ethionamide and Capreomycin), treatment duration and pyridoxine use were tested by bivariate analysis and shown to have association with occurrence of peripheral neuropathy. Dose of cycloserine, weight and area of residence (address) were tested in bivariate analysis have shown statistical association with psychiatric disorder. Duration of MDR TB treatment and alcohol drinking were tested using bivariate analysis and shown to have statistical association with hypothyroidism. Dose of capreomycin, treatment duration of MDR TB and weight are tested by bivariate analysis with occurrence hypokalemia and no statistical significance was seen.

**Table 7:** Bivariate analysis of drug related and sociodemograghic factors related with occurrences of adverse drug reactions, ALERT hospital, Ethiopia, April 2014 (n= 117)

| Variables | | Peripheral neuropathy | | | |
|---|---|---|---|---|---|
| | Categories | Yes (%) | No (%) | COR (95%CI) | P-values |
| **Age (years)** | 2-35 | 19 (76) | 74 (80.4) | 0.77 (0.269,2.207) | 0.627 |
| | ≥36 | 6 (24) | 18 (19.6) | 1 | |
| **Cycloserine dose** | 250-500 | 2 (8.0) | 33 (35.9) | 1 | |
| | 750-1000 | 23 (92.0) | 59 (64.1%) | 6.43 (1.426, 29.012) | 0.015 |
| **Ethionamide dose** | 250-500 | 3 (12.0) | 33 (35.9) | 1 | |
| | 750-1000 | 22 (88.0) | 59 (64.1) | 4.10 (1.142, 14.742) | 0.031 |
| **Pyrazinamide dose** | 200-1750 | 12 (48.0) | 62 (67.4) | 1 | |
| | 2000-2500 | 13 (52.0) | 30 (32.6) | 2.23 (0.182,1.096) | 0.078 |
| **Capreomycin dose** | 150-750 mg | 11 ( 44.0) | 62 (67.4) | 1 | |
| | 765-1000 mg | 14 (56.0) | 30 (32.6) | 2.63 (1.067,6.483) | 0.036 |
| **Duration of treatment** | 4-12 | 5 (20.0) | 44 (47.8) | 1 | |
| | > 12 | 20 (80.0) | 48 (52.2) | 3.66(1.268, 10.604) | 0.016 |
| **Vit.B6** | Yes | 10 (40.0) | 58 (63.0) | 1 | |

| | | | | | |
|---|---|---|---|---|---|
| **prophylaxis** | No | 15 (60.0) | 34 (37.0) | 2.55 (1.035, 6.327) | 0.042 |
| | Yes | 4 (16.0) | 6 (6.5) | 2.73 (0.706,10.554) | 0.145 |
| **Alcohol use** | No | 21 (84.0) | 86 (93.5) | 1 | |
| | | **Psychiatric disorder** | | | |
| | | **Yes (%)** | **No (%)** | | |
| **Age (years)** | 2-35 | 26 (81.2) | 67 (78.8) | 1 | |
| | ≥36 | 6 (18.8) | 18 (21.2) | 0.859 (0.307,2.404) | 0.772 |
| **Cycloserine dose** | 250-500 | 4 (12.5) | 31 (36.5) | 1 | |
| | 750-1000 | 28 (87.5) | 54 (63.5) | 4.019 (1.289,12.526) | 0.016 |
| **Duration of treatment** | 4-12 | 11 (34.4) | 38 (44.7) | 1 | |
| | >12 | 21 (65.6) | 47 (55.3) | 1.54 (0.663,3.595) | 0.314 |
| **HIV/AIDS** | Yes | 2 (6.2) | 14 (16.5) | 2.95 (0.633,13.822) | 0.168 |
| | No | 30 (93.8) | 71 (83.5) | 1 | |
| **Weight (kg)** | 7-45 | 6 ( 18.8) | 37 (43.5) | 1 | |
| | ≥ 46 | 26 (81.2) | 48 (56.5) | 3.34 (1.246,8.952) | 0.016 |
| **Address** | Addis Ababa | 26 (81.2) | 45 (52.9) | 3.85 (1.439,10.31) | 0.007 |
| | Others | 6 (18.8) | 40 (47.1) | 1 | |
| **Alcohol use** | Yes | 5 (15.6) | 5 (5.9) | 2.96 (0.796,11.026) | 0.105 |
| | No | 27 (84.4) | 80 (94.1) | 1 | |
| | | **Hypothyroidism** | | | |
| | | **Yes (%)** | **No (%)** | | |
| **Ethionamide dose** | 250-500 | 4 (19.0) | 32 (33.3) | 1 | |
| | 750-1000 | 17 (81.0) | 64 (66.7) | 2.12 (0.66,6.839) | 0.206 |
| **Pyrazinamide dose** | 200-1750 | 9 (42.9) | 65 (67.7) | 1 | |
| | 2000-2500 | 12 (57.1) | 31 (32.3) | 2.79 (1.066,7.333) | 0.037 |
| **Duration of treatment** | 4-12 | 2 (9.5) | 47 (49.0) | 1 | |
| | >12 | 19 (90.5) | 49 (51.0) | 9.11 (2.011,41.289) | 0.004 |
| **Age (years)** | 2-35 | 16 (76.2) | 77 (80.2) | 1 | |
| | ≥36 | 5 (23.8) | 19 (19.8) | 1.266(0.412,3.892) | 0.680 |
| **Sex** | Male | 15 (71.4) | 53 (55.2) | 1 | |
| | Female | 6 (28.6) | 43 (44.8) | 0.493 (0.176,1.379) | 0.178 |
| **Alcohol use** | Yes | 5 (23.8) | 5 (5.2) | 5.687 (1.476,21.910) | 0.012 |
| | No | 16 (76.2) | 91 (94.8) | 1 | |
| | | **Hypokalemia** | | | |
| | | **Yes (%)** | **No (%)** | | |
| **Capreomycin dose** | 150-750 | 64 (64.6) | 9 (50.0) | 1 | |
| | 765-1000 | 35 (35.4) | 9 (50.0) | 0.547 (0.199,1.504) | 0.242 |
| **Age (years)** | 2-35 | 77 (77.8) | 16 (88.9) | 0.438 (0.093,2.050) | 0.294 |
| | ≥36 | 22 (22.2) | 2 (11.1) | 1 | |
| **Weight (kg)** | 7-45 | 36 (36.4) | 7 (38.9) | 1 | |
| | 46-78 | 63 (63.6) | 11 (61.1) | 1.114 (0.397,3.127) | 0.838 |
| **Duration of treatment** | 4-12 | 45 (45.5) | 4 (22.2) | 1 | |
| | >12 | 54 (54.5) | 14 (77.8) | 0.343 (0.105,1.115) | 0.075 |

"1" Indicate the reference group COR = crude odds ratio CI = confidence interval A.A = Addis Ababa

The dose of individual drug was on "mg" and duration of MDR treatment by month

### 5.8 Multivariate results of drug related factors and sociodemograghic factors associated with adverse drug reactions

Cycloserine dose and area of residence (address) were independently associated with occurrence of psychiatric disorder by adjusting for initial weight of patients, alcohol drinking and HIV/AIDS co-morbidity. Patients who were taking higher Cycloserine dose (750-1000 mg/day) were 3.33 times more likely to develop psychiatric disorder than those taking lower dose (250-500 mg/day) (AOR=3.33, 95% CI (1.026, 10.827)). Patients residing at Addis Ababa were 3.44 times more likely to develop psychiatric disorder than those from other parts of country (AOR=3.44, 95% CI (1.245, 9.524).

Adjusting for doses of drugs (Cycloserine, Ethionamide, capreomycin and Pyrazinamide), duration of MDR TB treatment and alcohol drinking pyridoxine preventive therapy was independently associated with reduced occurrence of peripheral neuropathy. Compared with patients who were taking pyridoxine preventive therapy individuals who were not taking pyridoxine were 3 times more likely to develop peripheral neuropathy (AOR=3.08, 95% CI (1.179, 8.089).

Adjusting for sex, alcohol drinking, dose of ethionamide and dose of pyrazinamide treatment duration of MDR TB was independently associated with occurrence of hypothyroidism. Patients who were taking ethionamide containing MDR regimen for more than twelve months were 7.76 times more likely to develop hypothyroidism than those who were taking for less than or equal to twelve months (AOR= 7.76, 95% CI (1.635, 36.508) (Table 8 below)

**Table 8:** Multivariate results for drug related and Sociodemograghic factors independently associated with ADRs among patients treated for MDR TB at ALERT hospital, Ethiopia, April 2014 (n= 117)

| Variables | | Psychiatric disorder | | | |
|---|---|---|---|---|---|
| | | **Yes (%)** | **No (%)** | **AOR (95% CI)** | **p-value** |
| **Cycloserine dose** | 750-1000 mg | 28 (87.5) | 54 (63.5) | 3.33 (1.026,10.827) | 0.045* |
| | 250-500 mg | 4 (12.5) | 31 (36.5) | 1 | |
| **Address** | Addis Ababa | 26 (81.2) | 45 (52.9) | 3.44 (1.245,9.524) | 0.017* |
| | Out of AA | 6 (18.8) | 40 (47.1) | 1 | |
| **HIV/AIDS** | Yes | 2 (6.2) | 14 (16.5) | 0.512 (0.099,2.660) | 0.426 |
| | No | 30 (93.8) | 71 (83.5) | 1 | |
| **Alcohol use** | Yes | 5 (15.6) | 5 (5.9) | 0.489 (0.123,1.940) | 0.309 |
| | No | 27 (84.4) | 80 (94.1) | 1 | |
| | | **Hypothyroidism** | | | |
| | | **Yes (%)** | **No (%)** | | |
| **Sex** | Male | 15 (71.4) | 53 (55.2) | 1 | |
| | Female | 6 (28.6) | 43 (44.8) | 2.482 (0.813,7.580) | 0.110 |
| **PZA dose** | 200-1750 | 12 (48.0) | 62 (67.4) | 1 | |
| | 2000-2500 | 13 (52.0) | 30 (32.6) | 1.733 (0.597,5.029) | 0.312 |
| **ETH dose** | 250-500 | 4 (19.0) | 32 (33.3) | 1 | |
| | 750-1000 | 17 (81.0) | 64 (66.7) | 1.136 (0.298,4.324) | 0.852 |
| **Alcohol use** | Yes | 5 (23.8) | 5 (5.2) | 0.279 (0.067,1.165) | 0.080 |
| | No | 16 (76.2) | 91 (94.8) | 1 | |
| **Duration** | >12 months | 19 (90.5) | 49 (51.0) | 7.76 (1.653,36.508) | 0.009* |
| **of treatment** | 4-12 months | 2 (9.5) | 47 (49.0) | 1 | |

**Table 8 continued …**

| | | Peripheral neuropathy | | | |
|---|---|---|---|---|---|
| | | **Yes (%)** | **No (%)** | | |
| **Pyrazinamide dose** | 200-1750 | 12 (48.0) | 62 (67.4) | 1 | |
| | 2000-2500 | 13 (52.0) | 30 (32.6) | 0.375 (0.024,5.807) | 0.483 |
| **Capreomycin dose** | 150-750 mg | 11 ( 44.0) | 62 (67.4) | 1 | |
| | 765-1000 mg | 14 (56.0) | 30 (32.6) | 1.196 (0.424,3.377) | 0.735 |
| **Duration of treatment** | 4-12 | 5 (20.0) | 44 (47.8) | 1 | |
| | > 12 | 20 (80.0) | 48 (52.2) | 2.41(0.781,7.472) | 0.126 |
| **Vit.B6 prophylaxis** | Yes | 10 (40.0) | 58 (63.0) | 1 | |
| | No | 15 (60.0) | 34 (37.0) | 3.08 (1.179,8.089) | 0.022* |
| **Alcohol use** | Yes | 4 (16.0) | 6 (6.5) | 0.584 (0.136,2.509) | 0.470 |
| | No | 21 (84.0) | 86 (93.5) | 1 | |

*statistically significant

"1" Indicate the reference group, AOR = adjusted odds ratio CI = confidence interval A.A = Addis Ababa

The dose of individual drug was on "mg" and MDR treatment duration measured by month

# CHAPTER SIX: DISCUSSION

One of the major concerns about second-line anti-TB drug is their potential to cause adverse effects. The occurrence of adverse drug reactions could be a great challenge in controlling the MDR TB as it may compromise the patients' adherence to the treatment. In the current study total of 317 adverse drug reactions were experienced by almost all patients, 99.14% (116/117 patients). This is too high compared with similar studies from Lima (Peru) where 52% (20); Istanbul (Turkey) where 55.6% (15); Tomsk (Russia) where 73.3% (17) and South Africa where 80.6% (12) of patients experienced adverse drug reactions. But it is relatively similar to studies from Namibia where 90 % (11); Southern Africa (Lesotho) where 92% (19) and Philippines where 96% (16) of MDR TB treated patients developed drug related reactions.

The most frequently experienced adverse reactions in this study were hypokalemia 84.6%, gastrointestinal adverse effects 59.83%, psychiatric disorders 28.2%, arthralgia 26.5%, peripheral neuropathy 21.4% and hypothyroidism 17.95%. The incidence of hypokalemia in this study is very high compared with other studies from Southern Africa (Lesetho) where 42% (19); Tomsk (Russia) where 33.2% (17); Lima (Peru) where 31.3% (22) and Mumbai (India) where 31% of patients experienced hypokalemia (18). This might be due to; exhaustive follow up of serum potassium for every patient in the inpatient settings where all patients took injectable drug as admitted, the variations in the serum potassium cut point value used and the non consistency of capreomycin use as injectable alternative. Some studies used serum potassium below 3.0 mmol/dl (17-19) but in this study serum potassium level below 3.5 mmol/dl used to define hypokalemia. Among studies reported hypokalemia about 7-63% of patients involved in the studies (11, 16-18, 22) used capreomycin, the drug commonly responsible but in the current study all patients used capreomycin.

Gastrointestinal adverse effects were the second commonly encountered adverse reactions in this study which is similar to the findings reported from Philippines (16) where 61% and Namibia where 64% (11) of patients experienced gastrointestinal side effects. In addition, psychiatric disorders required frequent changes in MDR regimens, usually involving the temporary suspension of the culprit drug (cycloserine in the case of psychosis and depression). Thirty three patients (28.2%) developed psychiatric disorders which is similar to the studies from Turkey where 27% (15) and Mumbai (India) where 28% (18) of patients developed the drug related psychiatric problems. In

contrary to current study findings studies from Philippines and Lima (Peru) reported 49% (16) and 36.7% (30) of patients developed psychiatric disorders respectively. The other adverse drug reactions occurred are consistent with reported by different literatures as shown in the table below.

**Table 9:** Frequency of adverse drug reactions occurred among patients treated for MDR TB at ALERT hospital versus frequency reported by literatures

| **Adverse drug events** | **ADRs developed among patients in ALERT hospital** **%** | **Reported in literatures from different studies** **%** |
|---|---|---|
| Hypokalemia | 84.6 | **6 – 42** *(15-19, 22)* |
| Gastrointestinal adverse effects | 59.83 | **20.5 -100** (11, 12, 17, 18, 21, 30, 40) |
| Psychiatric disorder | 28.2 | **15.6 - 49** *(15, 16, 18, 19, 21, 30)* |
| Arthralgia | 26.5 | **3.1 -47** (11, 16-18, 21, 26) |
| Peripheral neuropathy | 21.4 | **7.9 – 51** (12, 16, 18, 19, 26, 30, 41) |
| Hypothyroidism | 17.95 | **3.5 – 53.6** (17, 18, 26, 30, 34) |
| Dermatological effects | 5.98 | **4.6 – 43.3** (11, 12, 26, 30) |
| Renal toxicity | 5.1 | **3.3 – 21** (17-19, 30) |
| Visual disturbances | 3.42 | **4.4 – 6** (13, 26) |
| Hepatotoxicity | 2.6 | **0 – 16.8** (17, 18, 26, 30, 42) |

All adverse drug reactions were initially tried to be managed symptomatically. Supplementation of potassium chloride tablets or IV was commonly used for hypokalemia or dose reduction and suspension of culprit agent (capreomycin). Psychosis was one of the frequently encountered events and managed with antipsychotic drugs and suspension and/or removal of the suspected agents (Cycloserine). Although every efforts were made to manage the adverse drug reactions the culprit drugs were permanently removed for 3.44% (4/116) of patients. Compared with other studies in the current study the suspected drugs were permanently removed for small number of patients, in Peru for 5% (24/466) (20); in Tomsk, Russia for 28.7% (70/244) (17); in India, Mumbai for 40% (18) and at DOTS-plus initiatives sites (Estonia, Latvia, Peru, Philippines and Tomsk Oblast) for 30% of patients (26) culprit drugs were permanently removed from regimens.

The life threatening adverse reactions caused offending drug/s dose reduction or temporary interruption for 27 patients (23.3%). The frequency of temporary interruption in the current study was greater than reported from Peru where for 11.6% (7/60) patients culprit drugs were suspended (30) but the highest rate of interruption was reported from Philippines cohort where for 49% of patients the suspected drugs were temporarily discontinued (16). Despite the treatment period of MDR TB was not completed in this study most of patients (58.6%) who developed adverse reactions were resolved without permanent disability which is in line with most of literatures (3, 11, 17).

Two deaths occurred in this study (1.72%) related with adverse drug reactions, one patient developed severe hypokalemia (with serum $K^+ < 2.4$ mmol/l) and renal toxicity and the other patient developed hepatotoxicity and hypokalemia. Compared to studies from South Africa where 6 deaths (9%) associated with hypokalemia or renal toxicity (27) and 4 deaths (6%) attributed to hypokalemia or hypomagnesemia (25) the death occurred in this study was low even if adverse reactions frequently occurred. Two patients (1.7%) stopped treatment after developing adverse drug reactions which is in line with study conducted at DOTS-plus initiative sites where 0-8.2% of patients on treatment stopped entire drugs (26).

Patients who were taking higher doses of cycloserine (750-1000 mg/day) were 3.33 times more likely to develop psychiatric disorder than those took lower doses, 250-500 mg/day (AOR=3.33). Similar to this study different studies reported that higher cycloserine dose administration could cause psychiatric disorders (17, 18, 31). Patients residing Addis Ababa were more likely to develop psychiatric disorder than those from other parts of country (AOR=3.44). The experience of insecurity and hopelessness, rapid social change and the risks of violence and physical ill-health may explain the greater vulnerability to common mental disorders (43).

Patients who were not taking pyridoxine preventive therapy were 3 times more likely to develop peripheral neuropathy than patients who took pyridoxine (AOR=3.08). The national guideline for drug resistant TB also recommends that for every 250 mg of cycloserine prescribed 50 mg of pyridoxine should be supplemented (28). Some literature reported that co-administration of pyridoxine was preventive for patients taking isoniazid but no studies reported preventive effects of pyridoxine co-administration with ethionamide or cycloserine (44).

Treatment duration of MDR TB more than 12 months was independently associated with occurrence of hypothyroidism. Patients who were taking ethionamide containing MDR regimen for more than twelve months were 7.76 times more likely to develop hypothyroidism (AOR= 7.76). This is similar to studies conducted at Mumbai (India) and Lima (Peru) where prolonged exposure to second line drugs increased the incidence of hypothyroidism (18, 30).

# CHAPTER SEVEN: LIMITATIONS OF THE STUDY

## Limitations

Data were collected retrospectively through chart review and under-reporting or over-reporting as well as reporting biases are all possible, especially for events not defined by laboratory criteria

Small number of the patients involved in the study. So it limits the inferences of the study findings to the general population.

# CHAPTER EIGHT: CONCLUSSION AND RECCOMMENDATIONS

## 7.1 CONCLUSSION

The adverse drug reactions related with MDR TB treatment were commonly encountered among patients involved in the study. Hypokalemia and gastrointestinal adverse effects were among the frequently reported adverse reactions.

The adverse drug reactions caused two deaths, two permanent drug discontinuation and four offending drug removal from drug regimen.

Dose reduction, temporary discontinuation and removal of culprit drugs from regimen or specific symptomatic management were the commonly used intervention followed by the clinicians.

Higher doses of cycloserine and residing in Addis Ababa were independently associated with psychiatric disorders. Pyridoxine preventive therapy reduced the incidence of peripheral neuropathy. Treatment duration of MDR TB more than twelve months was independently associated with the occurrences of hypothyroidisms.

## 7.2 RECCOMMENDATIONS

Based on the study findings the following recommendations forwarded to increase the success of MDR TB treatment.

**To ALERT hospital:**

1. Patients who start MDR TB treatment on similar standardized drug regimen just used in this study would experience similar drug related adverse reactions and needs close monitoring.
2. Suspending the suspected drugs or all MDR drug regimens could cause drug resistance and compromise therapeutic resources available to treat the infection. So it is advisable to initiate treatment with the lower recommended doses (for example cycloserine) and develop strategies to aggressively manage the symptoms.
3. Patients who were taking higher cycloserine doses were more likely experienced psychiatric disorders. Acute psychosis is one of the common events which caused dose reduction, suspension and removal of cycloserine from treatment regimen. So as to minimize this

adverse reactions patients who are candidate for higher dose needs to be closely followed and if necessary early initiation of antipsychotics might be warranted.

4. Patients supplemented with pyridoxine preventive therapy were less likely experience peripheral neuropathy. So pyridoxine co-administration should be encouraged. But it should be in mind that pyridoxine excessive dose can cause peripheral neuropathy.

5. Patients residing in Addis Ababa more likely experienced drug related psychiatric disorders in this study. Further observational study needed to explain the differences in incidence of psychiatric disorder among patients residing in Addis Ababa and other parts of country.

**To federal ministry of health (FMoH):**

1. MDR TB treatment in Ethiopia is commonly based on standardized treatment regimens. Adverse drug reactions experienced in these study individuals could be manifested similarly among patients who start treatment at other MDR TB service providing sites. Guideline development for detection, management and follow up of MDR TB drug related ADR is required which could increase the patient compliance to the treatment regimen.

2. Adverse drug reactions caused drug discontinuation and removal of suspected agents from treatment regimens which might favor resistance to the drugs used in the country. So it is appropriate to use drug susceptibility testing for second line anti TB drugs used in our settings.

3. Community health workers might be crucial for identification and referral of some adverse drug reactions like psychiatric disorders which causes drug discontinuation and default from treatment. So it is highly recommended to train the community health workers to provide direct supervision of medications, to recognize early manifestations of adverse reactions and emotional support and counseling for patients and family members.

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# ANNEX: DATA COLLECTION TOOLS

**Instructions**

1. This data abstraction format is intended to use in the data collection process of assessing ADRs of MDR TB treatment among patients in ALERT Hospital
2. The format has four parts and part one consists of general information about the patient, part two is about patients treatment information, part three is concerned about patients drug related problems and part four is about patient's co-morbidity ,concomitant drug use and adherence assessment
3. Please read carefully and try to fill the requested data from the patient register and medication card or reporting form used as per the specific information requested
4. If there is any unclear or problem you encounter please ask the investigator as much as possible
5. Select from the alternatives the one or more which matches the data you get from the patient medical record

**Part I: General Information**

1.2 Age _____

1.2 Weight (kg) ----------

1.3 Sex A. Male B. Female

1.4 Address

A. Addis Ababa
B. Oromia
C. Tigray
D. SNNPR
E. Amhara
F. Others (specify) _____

1.5 Occupation

A. Student
B. Gove't employee
C. Merchants
D. Labor worker
E. Farmer
F. Others (specify) _____

1.6 Alcohol use A. Yes B. No

1.7 Smoking status A. Yes B. No

1.8 Educational status

1. Illiterate
2. Literate
3. Preschool age

1.9 Marital status

A. Married
B. single
C. Widowed
D. Divorced

**Part II: Patients treatment information**

2.1 Was the patient been treated for TB before?

A. Yes B. No

2.2 What is the treatment regimen the patient had used?

A. 2RHZE/ 4RH B. 2RHZ/4EH

C. 2RHZE/6EH D. Other (specify) _____

2.3 Was the patient confirmed of having MDR TB?

A. Yes B. No

2.4 What is the site of MDR TB infection?

A. Pulmonary TB B. Extra PTB

2.5 What are the spectrums of drug resistance the patient registered? (number and specific drugs for which the bacilli resistant) _____

2.6 What are the patient treatment regimens for MDR TB during

A. Intensive phase _____ B. Continuation phase _____

2.7 How long the patient was been in treatment for MDR TB (month)?

A. Intensive phase _____ B. Continuous phase _____

2.8 What is the treatment outcome of patient with MDR TB? _____

**Part III: Patient's drug related problems**

3.1 Is there any documented drug related adverse reactions?

A. Yes B. No

3.2 If yes, to the above question what is the adverse drug reactions occurred?

(Please, write) _____

3.3 Was the patient been on follow up to monitor the safety/ avoid any unwanted drug side effects?

A. Yes B. No

3.4 If "yes", to the above question please fill the following tables for the laboratory/clinical parameters that are monitored

| **Parameters monitored** | **Months of follow up** | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| Weight (kg) | | | | | | | | | | | | | | | | | | | | | | | | | |
| Scr (mg/dl) | | | | | | | | | | | | | | | | | | | | | | | | | |
| BUN | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALT | | | | | | | | | | | | | | | | | | | | | | | | | |
| AST | | | | | | | | | | | | | | | | | | | | | | | | | |
| TSH | | | | | | | | | | | | | | | | | | | | | | | | | |
| $K^+$ (mmol/dl) | | | | | | | | | | | | | | | | | | | | | | | | | |

3.5 What are the interventions done to the adverse drug reactions mentioned above (Q 3.2)?

A. Dose reduction of suspected drugs
B. Temporary withholding of the suspected drugs
C. Temporary discontinuation of all the drugs
D. The suspected drug changed
E. Increased laboratory monitoring
F. specific symptomatic management of the drug events

3.6 What are the most likely drug(s) that is/are identified during the follow up by the physician as cause of the reactions? _____

3.7 Was there any interruption (missing) of MDR TB drug related with the adverse drug events? A. Yes B. No

3.8 If the answer to the above question is yes, how many doses were missed (interrupted)? (Write the number of daily doses) _____

3.9 Which specific drug was interrupted because of the drug related adverse reactions?

_____

3.10 What was happened to the patient as result of adverse drug reactions?

A. Died due to the drug events
B. Permanent discontinuation of all drugs
C. Permanent sequale
D. Resolved without sequelae
G. Unknown

**Part IV: Co-morbid conditions and concomitant drug use**

4.1 Was there any Comorbid medical condition other than tuberculosis?

A. Yes B. No

4.2 If yes, to the above question what are the disease conditions the patient do have?

_____

4.3 Was the patient taking any medication for co-morbid condition in addition to drugs for MDR TB?

A. Yes B. No

4.4 If yes, to the above question what are these drugs? _____

**CERTIFICATE**

This is to certify that the thesis entitled "**Adverse drug reactions and associated factors among patients treated for Multidrug resistant tuberculosis in ALERT hospital, Addis Ababa, Ethiopia**" was carried out by **Tesfaye Demessie** under direct supervision of the advisor(s) listed below. Further, the advisor(s) certify that this work has not been submitted in part or full in any University or Institution for any Degree or Diploma.

1. Name: _____Signature: _____Date:_____
2. Name: _____Signature: _____Date:_____
3. Name: _____Signature: _____ Date: _____

**DECLARATION**

I hereby declare that the work embodied in this thesis was carried out by me under direct supervision of **Mr. Belay Yimam** and **Mr. Tsegaye Tewolde** from College of Public Health and Medical Sciences, Jimma University and **Dr. Tesfamariam Mebrahtu** from ALERT hospital. This work has not been submitted in part or full in any University or Institution for any Degree or Diploma. I further endorse that this work is the property of Jimma University and all rights in this regard are reserved with Jimma University.

Name: _____Signature: _____Date:_____