ADDIS ABABA UNIVERSITY

ADVERSE DRUG REACTIONS AND ASSOCIATED CLINICAL OUTCOMES IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS: A FACILITY-BASED RETROSPECTIVE COHORT STUDY IN ADDIS ABABA, ETHIOPIA

BY:

Dr. Bisrat Solomon, MD

Academic Advisors:

Dr. Tsegahun Manyazewal, Ph.D.

Dr. Yimtubezinash Woldeamanuel, MD, Ph.D.

A Research thesis submitted to Addis Ababa University, College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trial for Africa (CDT-Africa), in partial fulfillment of the requirements for the Master of Science in Clinical Trials

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DECLARATION

ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, CENTER FOR INNOVATIVE DRUG DEVELOPMENT AND THERAPEUTIC TRIAL FOR AFRICA (CDT-AFRICA)

ADVERSE DRUG REACTIONS AND ASSOCIATED CLINICAL OUTCOMES IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS: A FACILITY-BASED RETROSPECTIVE COHORT STUDY IN ADDIS ABABA, ETHIOPIA

I the undersigned have declared that this thesis entitled: ADVERSE DRUG REACTIONS AND ASSOCIATED CLINICAL OUTCOMES IN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS: A FACILITY-BASED RETROSPECTIVE COHORT STUDY IN ADDIS ABABA, ETHIOPIA is my original work and has not been presented for a degree in any university. Furthermore, all the sources of information and materials have been acknowledged through referencing.

Dr. Bisrat Solomon	Signature	Date

Approved by the Examining Boar

Chairman, Dep. Graduate Committee	Signature	Date
Dr. Tsegahun Manyazewal, PhD	Signature	Date
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External Examiner	Signature	Date

Contents

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ACRONYMS AND ABBREVIATIONS

ADR……..…….……..….Adverse Drug Reaction

AE…….. Adverse Event

AKI…….…….Acute kidney Injury

ALERT……..Africa Leprosy Rehabilitation and Training Center

ALT……...…….. Alanine Aminotransferase

ALP……. Alkaline Phosphatase

Am…….……..Amikacin

AST……..…… Aspartate Aminotransferase

AZT……...……Zidovudine

BMI…….……...…….Body Mass Index

BPal…….…….Bedaquline pretomanid, Linezolid

CFZ…….…….Clofazimine

Cm……..Capreomycin

COPD…… Chronic Obstructive Pulmonary Disease

Cs…….…….……Cycloserine

DM…….…… Diabetes Mellitus

Dlm……Delamanid

DRTB…….…….. Drug Resistant Tuberculosis

DST……..…….Drug Susceptibility Test

E……………………..……………………………………………………………… Etahmbutol

Eto…..…………………….……………………………………….……………………..Ethiomanid

FQ……………………………………………………………………………….Fluoroquinolones

GI…………………………………………………………………….…… Gastrointestinal

HIV…………………………………………………………... Human Immunodeficiency Virus

HTN…………………………………………………….…………………….………… Hypertension

INH…………………..…………………………………………………………….. …Isoniazid

Km……………………………………………………………...................................kanamycin

Lfx…………………………………………..………………………………….Levofloxacin

LTFU………………………………………………………..………………... Loss To Follow Up

Lzd……………………..…………………………..……………………………………..Linezolid

MDR TB……………………………………..……………Multi Drug Resistant Tuberculosis

Mfx………………………………………………..…..………………..…………Moxifloxacin

NICU,,,,,,,,,.…….,,,,,,,,,,,,…,,Neonatal intensive care unit

NTP……………………………………..……………National Tuberculosis Programme

PAS…………………………………………..…………...………Paraminosalicylic Acid

Pto………………………………………………………………………………..Pretomanid

R……………………………,,,…….,…..Rifampicin

RR-TB…………………………………………………… Rifampicin Resistance Tuberculosis

S……..……..……...Streptomycin

TB……..Tuberculosis

TSH ……..……...……Thyroid Stimulating Hormone

UMC……..……...……Uppsala Monitoring Centre

WHO…….……World Health Organization

Z……..……..…….……..Pyrazinamide

SUMMARY

Background; Drug-resistant Tuberculosis (DR-TB) poses a significant global public health threat, with adverse drug reactions (ADRs) during treatment complicating medication outcomes and leading to substantial mortality. In Ethiopia, despite a high prevalence of DR-TB, there have been limited studies on ADRs during treatment and their effects on patient outcomes.

Objective; This study aimed to assess the incidence, clinical outcomes, and risk factors associated with ADRs in the treatment of patients with DR-TB in Addis Ababa, Ethiopia.

Methods: A facility-based, retrospective cohort study was conducted on patients with DR-TB who were followed up in two major DR-TB treatment sites, the St. Peter's Specialized Hospital and the ALERT Comprehensive Specialized Hospital, in the years 01 January 2017 to 31 December 2023. Records of the patients were monitored throughout their treatment time. Information on ADR diagnosis, laboratory findings, clinical observations, type of second-line anti-TB regimen, type and nature of the DR-TB, presence of co-morbidities such as HIV, hypertension, diabetes mellitus, chronic obstructive pulmonary diseases, and asthma, and sociodemographic characteristics were abstracted from patients' charts and registries. The World Health Organization - Uppsala Monitoring Center (WHO-UMC) system was employed for standardized causality assessment of ADRs. Multivariate Cox regression analysis was employed to identify factors associated with ADRs. Survival among predictor variables was assessed using Kaplan-Meier (KM) curves. Adjusted hazard ratios (AHR) with their corresponding 95% confidence intervals (CI) were estimated, and statistical significance was declared for a $p\text{-value} < 0.05$.

Result: A total of 292 patients with DR-TB were included, with a median age of 30 years [interquartile range (IQR) = 29–32], 161 (55%) male, and 113 (38%) had comorbidities. Cases were mainly rifampicin-resistant [281(96%)], pulmonary TB [225 (77%)], and on long-term regimens with new drugs [173 (59%)]. Drugs identified during treatment were Levofloxacin, Moxifloxacin, Bedaquiline, Linezolid, Clofazamine, Cycloserine, Caperomycin, Proteonamid, pyrazinamide, Ethambutol, Isonaizid, Ethionamide, and Kanamycin. The overall incidence of ADRs was 8.10 per 100 person-month (PM) (95% CI: 7.02-9.36) during a total follow-up time of

2294 months. The most frequently reported ADRs were gastrointestinal disturbance (31.9%), followed by peripheral neuropathy (21.9%), and arthralgia (17.5%). Temporary and permanent drug discontinuation were noted in 17.1% and 21.9% of patients, respectively. Predictors of ADRs were hospitalization (AHR = 1.53, 95% CI: 1.10-2.13), baseline anemia (AHR = 1.58, 95% CI: 1.16-2.17), the age group of 25-49 years (AHR =1.53, 95% CI: 1.05-2.21), and older age above 50 years (AHR = 1.87, 95% CI: 1.19-2.93). Good treatment outcome was observed in 76% of cases, with no significant association found between ADRs and treatment outcomes.

Conclusion: In this study involving patients with DR-TB, over half of the participants encountered at least one ADR. Patient admission, baseline anemia, and older age were identified as predictors of ADRs during MDR-TB treatment. Particular emphasis should be placed on these susceptible groups to facilitate early prediction, prompt management, and the formulation of appropriate treatment regimens that address ADRs effectively.

Keywords: Adverse drug reaction, drug-resistant tuberculosis, treatment outcome, Ethiopia

1. INTRODUCTION

1.1. Background

Tuberculosis (TB) is a major public health problem and its treatment has become challenging due to the emergence of resistance to anti-TB medications. Resistance to one first-line anti-TB drug is a monoresistance, resistance to more than one first line anti TB drug, other than both isoniazid and rifampicin is polyresistance, while Multidrug resistance (MDR-TB) is resistance to at least both rifampicin and isoniazid. (1) Globally in 2022 there were an estimated 10.6 million cases and 1.3 million deaths due to TB. Additionally 410 000 people developed rifampicin-resistant TB (RR-TB) or MDR TB. (2) According to the 2023 WHO African region progress report, Africa accounted for 23% of TB cases and 31% of TB related deaths and Ethiopia is still one of the 30 high-burden TB countries. (3)The prevalence of any anti-TB drug resistance in Ethiopia is 14.62%, while MDR TB prevalence is 10.78%. (4)

DR-TB treatment is challenging due to the interplay of different factors but adequate treatment and monitoring can be effective to cure TB. TB treatment goals include decreasing transmission, curing the patient, preventing death from TB disease and its late effects, preventing relapse, and the development of acquired drug resistance. (5, 6) DR Anti-TB drugs used in Ethiopia include shorter, all-oral bedaquilline-containing regimens, longer regimens, high-risk TB regimens and Bedaquline pretomanid, linezolid(BPal) regimens under operational research. These regimens are complex, taken for a longer duration and are associated with adverse drug reaction (ADR). ADRs can result in increased morbidity and mortality presenting a significant challenge to DRTB treatment. (5)

ADRs are harmful, unintended reactions to medicines that occur at doses normally used for treatment. (7) An adverse event (AE) is defined as any untoward medical occurrence that presents in a patient during treatment, but which does not necessarily have a causal relationship with the treatment. (8) Causality to an ADR can be done by assessing the timing of the event, response to withdrawal, the pattern of illness, rechallenge, and the results of investigations. (9) ADRs occur in more than half of patients on second-line TB drugs and are a major cause of poor adherence, treatment failure, and death. (10) Clinical and laboratory presentation of ADRs include mild gastrointestinal symptoms, arthralgia,

myalgia, .hepatotoxicity, ototoxicity, optic neuritis, hypokalemia, peripheral neuropathy, hypothyroidism, haematological disorders, psychiatric disorders, cutaneous ADR, nephrotoxicity and cardiotoxicity. Early identification with timely and appropriate management of ADRs is essential for a good treatment outcome. (11)

1.2. Statement of the problem

DR-TB is a major public health threat resulting in significant morbidity and mortality. Its treatment is challenging with various resistant patterns ranging from mono resistance to extensive drug resistance with a complex, long-term drug regimen. Although additional drugs have been introduced to broaden treatment modalities, intolerance and ADRs are affecting the subsequent treatment success rate. (12) Second-line anti-TB drugs are associated with ADRs that can lead to temporary treatment interruptions and permanent drug discontinuation, affecting compliance to treatment which can in turn influence treatment outcome. ADR are responsible for 28.7% of permanent drug discontinuation and 37.6% of temporary interruptions in DRTB patients. (13) In Ethiopia multidrug-resistant Tuberculosis (MDR) patients on treatment who had ADR are six times more likely to be lost to follow up which can subsequently increase community transmission and DR TB. (10) Adequate knowledge, appropriate monitoring and follow-up of ADR can improve treatment adherence and improve treatment outcomes. Multiple studies have shown ADRs can present with mild symptoms, but it can also result in organ damage, hospitalization, life-threatening condition or death. (11)

Although DR TB treatment regimens are highly associated with ADR, other possible sociodemographic, behavioural and clinical factors can increase patients' susceptibility to ADRs. Sociodemographic factors associated with ADRs include age, sex, and area of residence. (14, 15) Behavioural factors include smoking, alcohol use, and substance abuse. Clinical factors include obesity, anemia, human immunodeficiency virus(HIV) co-infection, pulmonary cavitation and Regimens containing aminoglycosides, linezolid, or pyrazinamide. (16, 17)

In Ethiopia, the national guideline on TB was revised in 2021 to incorporate new global recommendations on diagnostic, preventive and treatment modalities. The treatment modalities include all-oral Bedaqulline-containing Shorter regimens, BPal regimens and

modification on longer regimens. Additionally, guidance on early identification and management of Adverse effects is included. (5) There are few studies done on ADRs and adverse effects of DR TB treatment in Ethiopia. (14, 18, 19) In a study done in Addis Ababa Adverse events associated with MDR TB treatment was high, 92% of patients had at least one Adverse drug event during treatment. (20) After the introduction of Bedaqulline and Delaminid(Dlm) through the Ethiopian National TB Programme (NTP) in 2016, one study has shown an early result of Adverse effects to be 58.8%. (18) There is no recent study that shows ADRs during DRTB treatment, rather studies in Ethiopia have focused on adverse events during DR-TB treatment with results showing a wide discrepancy among each other. (21, 22) Therefore the aim of this study is to assess the incidence, impact and factors associated with ADRs of drug-resistant anti-Tuberculosis drugs in patients with DRTB at public hospitals in Addis Ababa.

1.3. Rationale of the study

MDR TB patients are already burdened with the disease, social stigma, full of fear and anxiety. Patients take multiple medications simultaneously for a relatively long period, and ADR occurs in more than half of patients with a negative impact on the compliance of treatment. Accurate bacteriologic diagnosis and compliance to treatment are key to successful treatment outcomes, but the occurrence of ADR are presenting as a major challenge towards successful MDR TB treatment. Multiple studies have shown ADRs are associated with unsuccessful treatment outcomes and loss to follow-up, which are a threat to the patient, the community and a setback to the reduction of TB incidence and death.

Identifying incidence, timing and associated factors of ADRs of DRTB drugs, can aid in the early prediction of ADRs in susceptible groups, timely management of ADRs, appropriate formulation of individualized treatment regimens by considering ADRs, close monitoring of ADRs in specific timings with preparation for higher centre care which can have a critical impact in improving treatment outcome. Improving adherence and treatment outcome will ultimately decrease community transmission, decrease the burden on the healthcare system and redirect resources to where they are more needed. It can also generate additional evidence to the existing pool of knowledge and will be an input to clinicians, treatment-initiating centres and the national TB program.

2. LITERATURE REVIEW

2.1. Adverse drug reactions

For decades DRTB has been a major hurdle for a successful TB treatment outcome. The existence of ADRs is an additional burden with prevalence as high as 92%. ADRs can be diagnosed with the clinical presentation of patients or may need laboratory tests. (20)ADRs such as gastrointestinal ADR, peripheral neuropathy, hematologic abnormality, psychiatric disorders, QT prolongation, hepatoxicity, nephrotoxicity, and hypothyroidism are discussed below.

2.1.1. Gastrointestinal ADRs

Almost all DRTB drugs cause Gastrointestinal(GI) ADRs and are one of the most common symptoms. The presentation might be mild symptoms with nausea, vomiting, epigastric pain or bloating, but might sometimes be life-threatening. (11) A study in China has shown that GIADRs resulted in hospitalization in 12.5% of patients. In a study done in the Philippines vomiting was severe enough to cause drug discontinuation. (23) In studies done in Ethiopia GI ADRs were seen in 40.2% to 82% of patients on during DR TB treatment. (19)

2.1.2. Peripheral neuropathy

Peripheral neuropathies are disorders of the peripheral nervous system characterized by numbness, paresthesias, pain, weakness, and loss of deep tendon reflexes. A variety of conditions can cause peripheral neuropathy, including second-line anti-TB drugs. (24)Linezolid,(Lzd), Cycloserine(Cs), streptomycin (S), kanamycin(Km), Capreomycin(Cm), Isoniazid(H), Fluoroquinolones(FQ), Pretomanid(Pto), Ethiomanid/Eto), Etahmbutol(E) can cause Peripheral Neuropathy. Lzd has been categorized as one of the effective group A drugs but is commonly associated with peripheral neuropathy and optic neuritis. A dose of 1200mg/ day is associated with peripheral neuropathy in 81% of patients while lowering daily doses to 300mg/day alleviated symptoms. (25) In Ethiopia one study assessed peripheral neuropathy and was seen in 9.4% of patients on second-line drugs, but regimen and timing weren't clearly stated. (14) High dose INH has also been associated with Peripheral Neuropathy and Clofazimine(CFZ) was associated with Peripheral neuropathy in a case series reports. (26)

Diagnostic methods for Peripheral Neuropathy include nerve-conduction studies and electromyography but are not usually available in resource-limited settings, but different simple screening tools to monitor toxicity can be used. (25) Additionally, comorbid conditions, treatment of comorbid conditions can result in Peripheral Neuropathy, therefore needs careful assessment of individuals to identify possible cause and manage accordingly. (26)

2.1.3. Haematologic abnormalities

LZD, CFZ, Paraminosalicylic acid (PAS), and FQ have been associated with hematologic abnormalities. LZD treatment of more than 2 weeks has been linked with ADR such as anemia, thrombocytopenia, leucopenia, and pancytopenia. LZD is associated with the suppression of bone marrow and the inhibition of the formation of platelets. In a study done in Indonesia prevalence of anemia, thrombocytopenia, and leukopenia was 29%, 3.2%, and 2.2% respectively. (27) In other studies thrombocytopenia occurred more frequently than others. In a clinical trial, myelosuppression occurred in 18% of patients on LZD. (5) These events can be dependent on the dose and are reversible with appropriate treatment including dose reduction, blood transfusion, or erythropoietin treatment depending on their clinical presentation. (27)

2.1.4. Hypokalaemia and nephrotoxicity

Amikacin (Am) and Cm are usually associated with hypokalemia. In a study done in Indonesia 60% of patients on Cm had hypokalemia. Adequate monitoring of serum electrolytes in these patients is essential. (28) In a study done in Ethiopia hypokalemia was found to be the most common adverse drug reaction occurring in 54.3% of patients. (14) Aminoglycosides can also result in renal wasting contributing to additional electrolyte abnormality. In studies done in India Aminoglycosides such as kanamycin(Km), Am, and Cm are associated with nephrotoxicity occurring in 1.2% to 6.7% of patients. (10) In Pakistan renal toxicity occurred in 2.7% of the patients. (29) In a study done in Ethiopia nephrotoxicity occurred in 15.86% of patients on regimens containing Cm. (14) In a study done in Ethiopia after the introduction of Bdq and Dlm renal toxicity was 3.3%. (18) WHO (World Health Organization) recommends restricted use of injectables but are still used in individualized regimens in DRTB patients with few

therapeutic choices. E, Z and Cs can also cause renal toxicity, while Newer drugs such as Bdq and Dlm are relatively safe in DR-TB patients with renal failure. (11)

2.1.5. Ototoxicity

Aminoglycosides are frequently associated with ototoxicity. S affects the vestibular system whereas Km and Cm affect the cochlear apparatus and an irreversible apoptotic hair cell damage in the cochlea leads to permanent hearing loss. (30) Aminoglycoside-induced ototoxicity is dose-dependent with a narrow therapeutic window and needs close monitoring. In India Ototoxicity occurred in as high as 25% of patients. (11) In Ethiopia decreased hearing status was seen in 8.3% of the patients on aminoglycosides. (19)

2.1.6. Psychiatric ADRs

Psychiatric symptoms may present with anxiety, headaches, insomnia, suicidal ideation, giddiness, mental disturbances, and lower threshold for seizures. (11) Cs is bactericidal or bacteriostatic, depending on its concentration, and is one of the group B drugs usually associated with psychiatric ADRs. (31) In a study in India psychosis is seen in greater than 10% of patients, while in Ethiopia in a study that studied adverse drug event 15.3% of patients had psychosis. (14, 32) Anxiety, headaches, and seizures have also been associated with Cs in 10% of patients. Other second-line drugs such as Eto, FQs less frequently cause dizziness, headaches, and insomnia. (11, 32)

2.1.7. QT prolongation

Many second-line anti-TB drugs such as Cfz, Bdq, Dlm, Levofloxacin(Lfx), and Moxifloxacin (Mfx) can cause prolonged QT interval. (5) Cardiac toxicity and prolonged QT interval were one of the most feared toxicities with the increasing usage of Bdq, Dld and other repurposed drugs such as Cfz and Lzd. In the END TB cohort, only 3% of patients developed QT interval prolongation from patients on Bdq and Dld containing regimens with 96% of patients on additional QT-prolonging drugs (Mfx, Lfx, Cfz). (33) Moxifloxacin is more likely to cause QT prolongation compared to levofloxacin. In Ethiopia, QT prolongation was observed in 16.7% which is higher than other studies. (18) In a study done in South Africa 4.3% had a QTcF >500 ms and 26.2% had a QTcF change >60 ms with no arrhythmias and cardiac deaths. It has been shown in multiple studies that

concomitant use of azoles, antipsychotics, and antinausea drugs can contribute to the increased odds of QT prolongation. (34)

2.1.8. Hepatotoxicity

Hepatotoxicity is diagnosed with an increased concentration of liver function marker proteins like aspartate aminotransferase (AST)/alanine aminotransferase (ALT), alkaline phosphatase (ALP), or total bilirubin. It usually presents with nausea, vomiting, and jaundice. (35) Hepatotoxicity occurs frequently with first-line drugs of H, R, Z and can be as high as 80%. Second-line anti-TB drugs such as FQs cause hepatotoxicity in 2% -3% but it more commonly occurs in combination with other drugs. Hepatotoxicity has been less frequently encountered in second -line drugs such as Cfz, Bdq, Dlm, and Lzd. (11) In most studies, hepatotoxicity has occurred during the intensive phase of treatment. In studies done in Ethiopia hepatotoxicity occurred in the intensive phase during the 8^{th} to 58^{th} day. After the introduction of the relatively newer drugs for DRTB a study in Ethiopia has shown that hepatotoxicity occurred in 3.3% of the patients, but the study had a small sample size. (18) Other studies in Ethiopia have focused on hepatotoxicity in drug- susceptible TB patients. (21, 36)

2.1.9. Hypothyroidism

Eto, Pto, and PAS are associated with hypothyroidism. In a systematic review of MDR TB patients, the pooled prevalence of hypothyroidism was 17.0%. The pooled prevalence of hypothyroidism in Africa, Asia, and Europe was 25.0%, 13%, and 9% respectively. In a study in Egypt it occurred in 9.4% of the patients on average within 6 months of initiating treatment. (37) In Ethiopia hypothyroidism occurred in 2.69% and 6.7% of the patients. (14, 18)

2.2. Factors associated with adverse drug reactions

MDR TB treatment has multiple challenges with ADRs associated with treatment being one of the most commonly encountered. A cocktail of drugs are administered in DR TB patients and are in need of appropriate monitoring of ADRs to improve compliance to treatment and improve treatment outcomes. (12) The Complex MDR TB regimens are highly toxic and have contributed to the poor treatment success rate, morbidity, and mortality. Identification of sociodemographic, clinical, and behavioral factors

predisposing DR TB patients to ADRs is essential to avert harmful consequences. (Figure 1). (12, 38)

Age is a factor that has been associated with ADRs. As age increases there is a reduction in the clearance rate of metabolized drugs, and changes in the hepatic blood flow distribution which commonly affects liver function. (39) There are studies implying no association between age and ADRs but Hepatotoxicity frequently occurs in the older age group as seen in studies done in Peru, Iran, and Ethiopia. (14, 15, 40) Some studies have also shown that women were more likely to develop ADRs due to hormonal changes and differences in drug metabolism. A study in Iran found that ADRs were 1.9 times higher in females compared to male patients, other studies shown no difference between males and females.(14)

Alcohol users are generally associated with poor adherence, poor treatment outcomes, relapse, and higher mortality in MDR TB treatment. Alcohol has the effect of weakening the immune system which can lead to susceptibility to other diseases or alteration in the pharmacokinetics of medications for TB treatment. (41) In a study in Europe alcohol abusers compared to non-drinkers had more severe and persistent toxicity and hepatotoxicity occurred more commonly. (42) Toxic reactions (predominantly hepatotoxicity) among the alcohol abusers are significantly more often likely than those among patients without alcohol abuse. Additionally, more severe and irremovable adverse effects were observed in individuals with alcohol abuse. (43) This contradicts a study done in Russia in which both the number and the severity of adverse events didn't differ significantly between drinkers and non-drinkers. (44) Additionally, smoking and substance abuse have been associated with adverse drug reactions. In a study done in Ethiopia history of baseline khat use was one of the predictors of adverse drug reaction during MDR TB treatment. (45)

The presence of comorbidities such as COPD, DM, HTN, HIV have been associated with ADRs. Studies done in Ethiopia and Iran have shown comorbidities were associated with ADRs during MDR TB treatment. It can partially be due to comorbidities compromising immunity. (14, 15) MDR TB patients may present with Anemia due to chronic illness, it can also occur as an ADR to Cs, E, Z, Cfz, Lfx, and Lzd but others have argued anemia is a risk factor for adverse drug reaction. A study in Peru has shown that anemic patients had twice the odds of adverse drug reaction compared to non-anemic ones. (40)

Malnutrition also affects the pharmacokinetics of drugs with changes in the distribution of volume, bioavailability, and drug elimination. In underweight patients distribution of volume may be increased in streptomycin and rifampicin and drug elimination decreased in H and S. (46) A study in Latvia has shown underweight patients are more likely to develop side effects, a study in Iran have also shown weight of 40kg was a risk for occurrence of ADR. (15, 47) Furthermore, obesity has an effect on drug metabolism. A study in Peru has shown body mass index(BMI) of greater than 25kg / m2 was associated with adverse reactions. (40)

Patients on anti-TB encounter a wide array of ADRs, which can be particularly worsened if patients are taking additional drugs. The additive effect can be concerning in patients taking LZd and Zidovudine (AZT), due to the combined effects of myelosuppression and periperhal nerve toxicity. (48) Additionally monitoring of QT prolongation is required in patients taking BDQ, Cfz, FQ and Dld. The drug-drug and drug-disease interactions should be taken in account to minimize ADRs, increase safety, and attain optimal response. (5)

2.3. Implications of adverse drug reactions

ADRs during MDR TB treatment have resulted in modification in a treatment regimen with temporary or permanent drug discontinuation, dose modification, poor drug adherence, permanent disability, or death. (49) One of the most common ADRs that resulted in treatment modification and permanent disability are gastrointestinal adverse drug reactions, peripheral neuropathy, ototoxicity, psychiatric disturbances, hepatotoxicity, and nephrotoxicity. (16)

GI disorders are one of the most common ADRs in MDR TB treatment. In Pakistan, symptomatic management of ADRs was the mainstay of treatment for gastrointestinal disorders except for diarrhoea in which temporary PAS discontinuation was needed . (49) Peripheral neuropathy is also a common ADR that can lead to irreversible damage linearly associated with dose. In a prospective study done in China linezolid was permanently discontinued in 14% and the dose was reduced to 300mg daily in 55% of patients. (25) Furthermore in Pakistan linezolid was temporarily discontinued for 2 weeks. (49)

In a study done in Russia that studied hepatotoxicity, medications were stopped in 0.9% of patients, but the treatment wasn't entirely discontinued. (44) Similarly in Pakistan ADRs didn't lead to permanent drug discontinuation but treatment regimen was modified in 11% of patients.

Injectable agents such as Am, Cm, and S are highly toxic and are gradually being replaced by new and repurposed drugs, but are still being used in DR TB patients with few therapeutic choices. A study in Ethiopia has shown injectables were discontinued due to ototoxicity and clinical nephrotoxicity in 0.9% and 5.3% of the patients, while injectables were switched in 5.3%. (22) In Pakistan ototoxicity has resulted in both dose reduction and regimen modification. Other studies have reported discontinuation of injectables as high as in 55% of patients. (49, 50) In a study done in Ethiopia after the introduction of the new and repurposed drugs 40% of patients on MDR TB treatment needed permanent discontinuation with treatment regimen modification and temporary interruption with treatment using ancillary drugs was seen in 14.3%. (18) In Ethiopia psychiatric disturbance was more prevalent and was the leading cause of treatment regimen modification. Similarly in Pakistan Cs was temporarily stopped, permanently discontinued and dose was reduced in 3,3and 5 patients respectively. (13, 49) In China incidence of short treatment interruption (≤14 days) was 37.6%, and serious interruption (>14 days) was 28.7%. ADR was the most prominent factor of treatment interruption accounting for 20.3% of serious interruptions. (13)

Adherence to medicine is crucial for a successful treatment outcome. WHO defines Medication adherence as the extent to which a patient's behavior corresponds with the prescribed medication dosing regimen, including time, dosing, and interval of medication intake. (51) The patient, the community, and the health care system as a whole are all impacted by non-adherence. Non-adherence is a danger for MDR TB patients since it can result in prolonged infectiousness and transmission, relapse, and increased resistance in the community. (10) The existence of more than one co-morbidity, patients in the continuation phase of chemotherapy, TB/HIV co-infection, health system, patient and socioeconomic features, inadequate awareness of TB and anti-TB therapy, alcohol intake, patients' experience of side effects, the distance of the home to the health facility, and

long waiting time before access to treatment are among the recognized predictors of non-adherence in Ethiopia. (52)

Loss to follow-up (LTFU) is concerning during TB treatment. Lost to follow-up is defined as `A patient whose treatment was interrupted for eight or more consecutive weeks after getting registered at a TB treatment center/reporting unit or who did not start anti-TB treatment for eight or more consecutive weeks.`(4) Factors associated with LTFU include age, gender, education, residence, ADRs, financial factors, behavioural factors, migration, and social stigma. (53, 54)

ADRs during DR TB treatment are associated with non-adherence and LTFU. Additionally, Patients with poor adherence are at risk for poor treatment outcome. In India ADRs were significantly associated with non-treatment adherence and defaulter outcome, but the cure rate was higher in patients with ADRs. (38) This can be due to closer follow-up and management of patients with ADRs. Furthermore, a study in Egypt has shown ADRs during treatment didn't affect treatment outcomes in individuals who are adherent to treatment. (37)

A study on hepatotoxicity during therapy conducted in Russia found no association between hepatotoxicity and a worsening of the therapeutic result. (44) A prospective cohort research in Brazil found that although ART patients with low CD4 counts were more frequently linked to hepatotoxicity, they had a higher likelihood of positive outcomes overall. According to a study conducted in Ethiopia, patients who had ADR had a six-fold higher chance of being lost to follow-up. (10) Furthermore, in Philippines high-severity vomiting was an ADR that was independently related to loss to follow-up. (23) Meanwhile, slightly different findings were obtained from other studies. According to research from Nigeria, Uganda, and India, there is no association between ADR and treatment non-adherence. (52) (53-55) In addition, a study in India suggested no significant association between ADR and unfavorable outcomes such as failed, died, loss to follow up, transferred out, and switched to Extensively Drug-Resistant. (56)

3. CONCEPTUAL FRAMEWORK

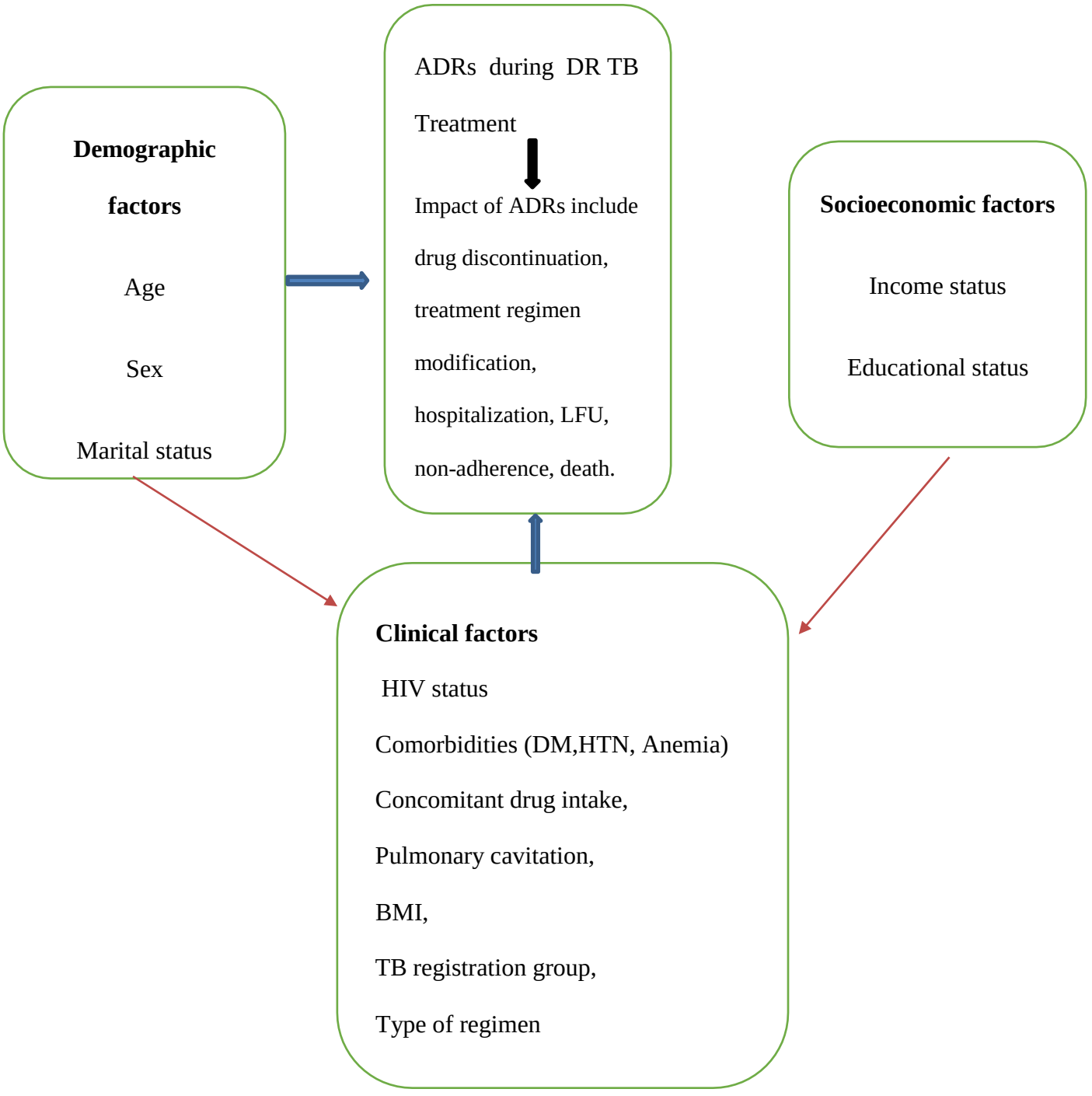

Figure 1 Conceptual Framework

4. RESEARCH OBJECTIVE

4.1. General objective

- To assess the incidence, clinical outcomes, and risk factors of ADRs in the treatment of patients with DR-TB in Addis Ababa, Ethiopia.

4.2. Specific objective

- To determine the incidence of ADR among patients on DRTB treatment.
- To assess the clinical outcomes associated with ADRs in patients on DRTB treatment.
- To assess the risk factors and impact of ADRs in patients on DRTB treatment.

5. METHODS AND MATERIALS

5.1. Study setting and context

The study was conducted in St. Peter's Specialized Hospital and ALERT Comprehensive Specialized Hospital (ALERT). St. Peter's specialized hospital was established on February 02, 1953, G.C. The hospital is located in Addis Ababa, gulele sub-city, wereda 01, 1.5 kilometers north of Shiromeda area. St. Peter's TB specialized hospital is currently one of the six hospitals administered by the federal ministry of Health, Ethiopia. Services given include internal medicine specialty and subspecialty services, TB/DRTB, maternal and child health, specialty and sub-specialty surgical services, adult/pediatric and neonatal intensive care unit (NICU) Services, interventional cardiology services, and others. (57) St. Peter's specialized hospital was chosen as the study area because the hospital serves more than 150,000 patients per year and is a catchment referral hospital to 3 primary hospitals and 12 health centres. It is also the first DR TB treatment site in Ethiopia and has served as a national referral centre for severe side effects during TB treatment with more than 10 years of experience. It has the necessary infrastructure with trained and experienced staff with a centre for research including clinical trials. (19)

ALERT is a hospital located in Addis Ababa, Kolfae Keraniyo sub-city. It originally specialized in leprosy but later expanded to include TB and DR TB treatment. MDR TB treatment was started in 2011 and was one of the first centrers to provide treatment using new and repurposed Anti TB drugs. Currently, it also has a research institute for TB research including clinical trials. It is a specialized treatment, research, and training resource centre focusing on leprosy, TB, HIV/AIDS, and other relevant infectious diseases.

5.2. Study Design

A facility-based retrospective cohort study was conducted using secondary data obtained from the two study sites, mainly TB patients' registries and patients' charts that document the follow-up of patients for ADRs beginning from the initiation of DR-TB treatment medications before they develop any ADRs.

5.3. Source population

All patients who were treated for DR TB were the source population.

5.4. Study population

The study population was patients who were treated with DR TB at the selected public hospitals in Addis Ababa in the years 2017 to 2023.

5.5. Inclusion and exclusion criteria

5.5.1. Inclusion criteria

Confirmed DR-TB patients of any age who were treated with DR-TB drugs were included in the study. Bdq and Dld were initiated in ALERT and St. Peter Specialized Hospital in 2017, and to include patients who were started on these drugs, patient charts starting from 2017 to 2023 were included in the study.

5.5.2. Exclusion criteria

Patients whose charts are incomplete for ADRs data, including missed follow-ups for major laboratory investigations recommended in the Ethiopian National TB treatment guidelines, were excluded. In addition, patients who had confirmed chronic kidney disease, hepatitis, hypothyroidism, and hearing loss prior to initiation of anti-DR-TB treatment were excluded.

5.6. Sample size determination

1- To determine the overall proportion of ADRs in DR TB patients.
Sample size was calculated by using the single population proportion formula. P (Overall proportion of ADRs in DR TB patients) = 0.724 from previous research done. (29)

The confidence interval was taken as 95% Power = 80%

$$\Rightarrow n = Z_{\frac{\alpha}{2}}^{2} \cdot \frac{P(1-P)}{d^{2}}$$

The sample size calculated using this method was 265. After adding a 10% non-response rate the sample size was 292. The sample size calculation for the overall proportion of ADR yielded a higher sample size. Therefore the final sample size was 291. It can also be calculated using EPI info (Figure 2).

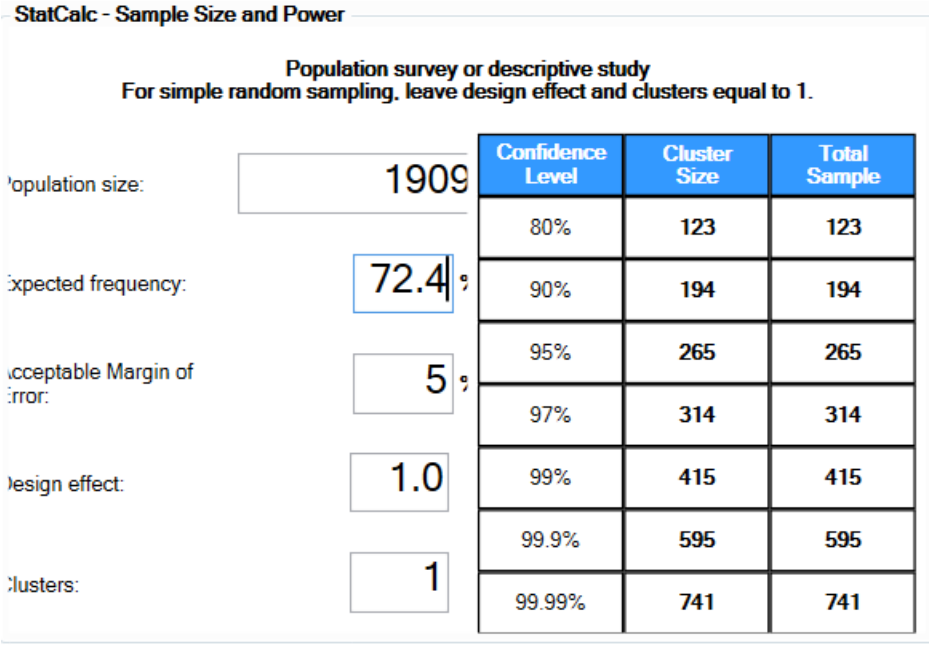

Figure 2. Sample size calculation for proportion of ADRs.

The sample size for factors associated with ADRs was calculated.

Weight greater than 40Kg was a factor associated with ADR. (29)

- In a previous study, 79.1% of patients with Weight greater than 40Kg had ADRs.
- The margin of error was taken as 5%.
- The confidence interval was taken as 95%
- power = 80%
- The sample size was 224. It can also be calculated using EPI info (Figure 3).

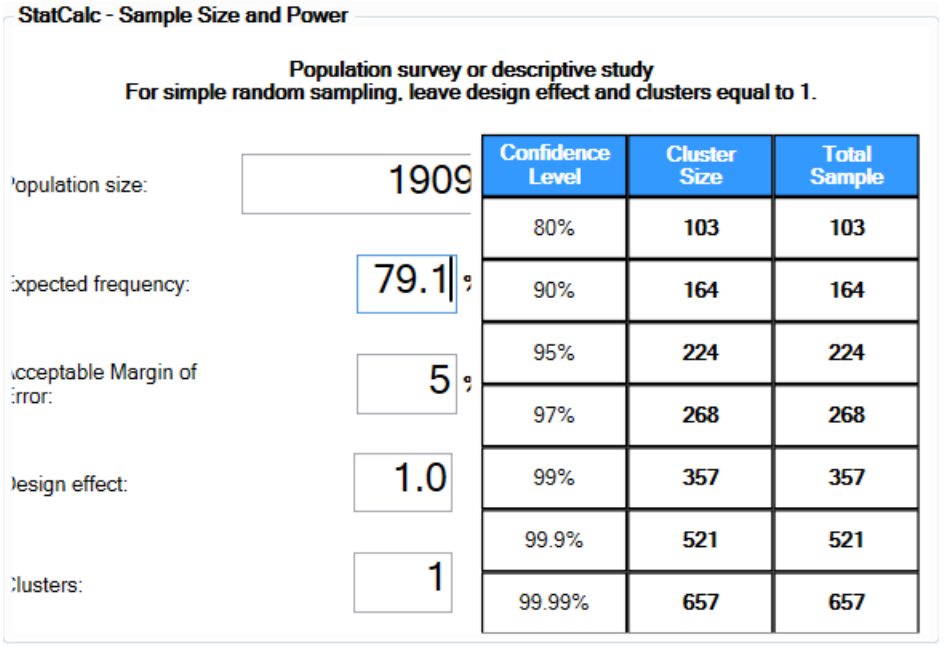

Figure 3. Sample size calculation for weight greater than 40 Kg.

Pulmonary cavitation is a factor associated with ADR.

- From a previous study, 86.3% of patients who had pulmonary cavitation had ADRs. (16)
- The margin of error was taken as 5%.
- The confidence interval was taken as 95%.
- Power = 80%.
- The sample size was 166. It can also be calculated using EPI info (Figure 4).

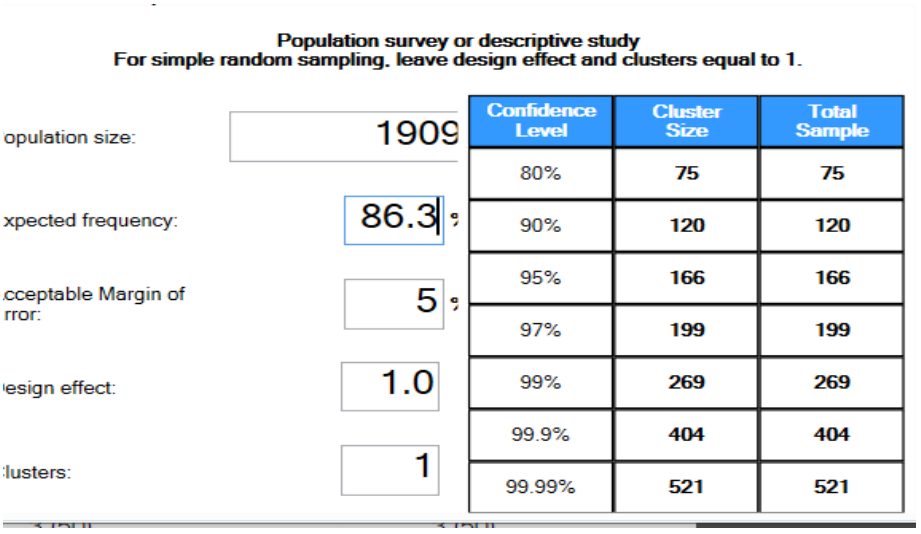

Figure 4. Sample size calculation for pulmonary cavitation.

5.7. Sampling technique

St. Peter's TB specialized hospital and ALERT hospital were chosen as the study area. Since 2017 in St Peter's Tuberculosis Specialized hospital, there were 534 patients enrolled for DRTB treatment. Since 2017 in ALERT there were 352 patients who were enrolled in the DRTB treatment. From the final calculated sample size of 292 proportional allocation was given to St Peter's Tuberculosis specialized hospital and ALERT hospital. The sample was proportionally allocated to each hospital (Figure 5).

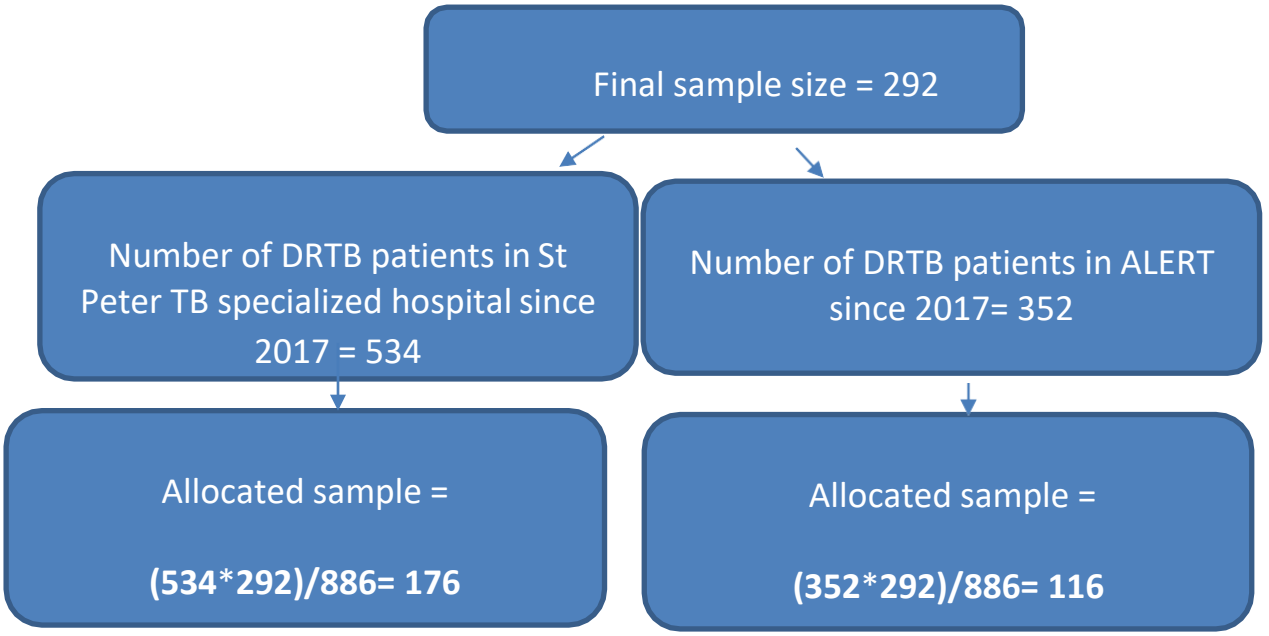

Figure 5 Sampling allocation flow chart.

From the final calculated sample size of 292 patients proportional allocation, given to St. Peters Specialized Hospital and ALERT H ospital resulted in 176 and 116 patients, respectively. Systematic random sampling technique was used to select study participants for all eligible DRTB patients registered. Since there were 534 patients enrolled in care at St. Peter Hospital, the allocated sample size was 176, K= 534/176= 3 by approximation, the first patient that was included in the study was the 3rd patient registered on the DRTB clinic registry and the rest was every 3 patients until we get a total of 176 samples. The same procedure will be used for ALERT hospital, there were approximately 352 DRTB patients on registry in follow-up care, so K= 352/116= 3, by approximation the first patient included in the study was the 3rd patient registered on the DRTB clinic registry, and the rest will be every three patients until a sample size of 116. Randomly selected patients who didn't fulfill the inclusion criteria were skipped, and sampling continued until the desired sample size of 292 was reached.

5.8. Methods of data collection

From the patients' charts, data on demographic, clinical, ADRs, and treatment outcomes (cured, treatment completed, treatment failure, LTFU) were collected using a standardized data abstraction form adapted from the WHO guidelines and previous literature. The medical records of those treated for DR-TB was obtained from the DR- TB clinic registries in the two study sites. A unique identifier was given, and the patient's name was not recorded on the data collection form. Training was given to data collectors on the objectives, data collection, and confidentiality of information. The questionnaire was prepared in the English language. Three data collectors who had a first degree in Medicine, Nursing, or Health Officer with a previous experience collecting such data were recruited. Supervision was done daily by the PI.

Laboratory test results, such as complete blood count, liver function tests, renal function tests, thyroid function tests, serum electrolytes, hepatitis, and HIV were collected as available. Details of ADRs were recorded, which were laboratory test results or clinical reports developed by the clinician handling the patient. One abnormal laboratory test was sufficient for a diagnosis of an ADR, where the WHO UMC (Uppsala Monitoring Center) system for standardized causality assessment was used.

5.9. Operational definitions and measurements

GI disturbances: are Nausea, vomiting, abdominal pain, diarrhea, reflux Hematemesis, melena, positive occult blood on stool analysis or by endoscopic study.

Hepatotoxicity: is a 3 times elevation in serum transaminases in the presence of symptoms to the upper limit of normal values or a five times elevated value of serum transaminases in the absence of symptoms.

Acute kidney injury (AKI): is creatinine level increased by (1.5–2.0) mg/dl above the baseline at any time during treatment.

Hypothyroidism: is at least one TSH (Thyroid Stimulating Hormone) value > 10 mIU/L after at least 3 months of second-line TB treatment.

Anemia: is defined as a hemoglobin value of less than 11mg/dl for females and less than 12 mg/dl for males.

Peripheral neuropathy: is a DR-TB patient presenting with tingling, numbness or burning in the trunk or extremities; diminished or absent reflexes; as diagnosed by the clinician or nerve conduction studies consistent with peripheral neuropathy.

Hypokalemia: is a serum potassium value lower than 3.0mEq/L.

Psychosis: was also defined as the presence of anxiety, hallucinations, insominia, depression, suicide, nightmares, or convulsions.

Hearing loss or vestibular disorders; are defined as Tinnitus or hearing loss confirmed by audiometry or diagnosed by a clinician.

Arthralgia; is defined as Presence of pain, swelling, or stiffness in the joints as reported by clinician.

Body mass index (BMI): is defined as severely underweight if BMI is <16·50, underweight when BMI is 16.5 - 18.49 kg/m2, normal if BMI 18.5–24.99 kg/m2, overweight and obese if BMI is greater than 24.99 kg/m2.

Cigarette smoking: is defined as patients who have previous history of smoking or who are currently smokers.

Alcohol consumption: is alcohol use or previous history of alcohol use as diagnosed by a treating health care professional.

New patients: are patients that have never been treated for TB or have taken anti-TB drugs for less than one month.

Previously treated patients: are patients who have received anti-TB drugs for one or more months in the past and have again been diagnosed with Tuberculosis.

Relapse cases: are patients who were declared cured or treatment completed at the end of their most recent treatment course, and are now diagnosed with a recurrent episode of TB irrespective of the duration of previous TB treatment completion.

Treatment after failure: refers to patients who were declared treatment failure in their most recent course of treatment as per national protocol and are now decided to be treated with a full course of TB treatment.

Treatment after loss to follow-up: refers to patients who were declared lost to follow-up at the end of their most recent course of TB treatment and are now decided to be treated with a full course of TB treatment.

Others: refers to patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented, or patients that do not fit into any of the categories listed above.

Cured: is 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 an intensive phase or during the last 12 months of treatment for patients on longer regimens.

Treatment completed: are those who completed treatment 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 an intensive phase or during the last 12 months of treatment for patients on longer regimens.

Treatment failure: 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 an intensive phase, or, evidence of additional acquired resistance to fluoroquinolone or other group A second line drugs, or, Adverse drug reactions.

Death: refers to a patient who died during TB treatment.

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

Not evaluated: is a TB patient for whom no treatment outcome is assigned as "transferred out" cases with unknown outcomes at reporting unit.

Treatment adapted: is an RR-/MDR-TB patient registered to second-line TB treatment and whose current empirical treatment regimen was ended due to DST (Drug Susceptibility Test) results showing resistance to second-line drugs and therefore rendering the current treatment sub-optimal or ineffective before the end of intensive phase/before the last 12 months of treatment for patients on longer regimens.

Good treatment outcome: are patients who have completed treatment or are cured.

Poor treatment outcome: is the occurrence of treatment failure, death or lost to follow-up.

Serious adverse event: are those leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly; or AEs that require an intervention to prevent such an outcome from happening are included.

5.10. Variables

5.10.1. Dependent variable

The dependent variable was ADR.

5.10.2. Independent variable

Independent variables were socio-demographic variables including age, sex, marital status, residence, religion, educational status, and occupation, clinical factors including type of TB, previous history of TB treatment, Body Mass Index (BMI), baseline haemoglobin level, the type of second-line regimen, HIV infection, and presence of other co-morbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary diseases and asthma.

5.11. Data quality control and Management

The collected data was transferred manually to a computer and cleaned. The cleaned data were exported to STATA for analysis. The data were checked for accuracy, completeness, and consistency, and the errors were corrected. Training was given to data collectors on the objectives and relevance of the study, data collection, and confidentiality of information. Pretesting of the questionnaires were done by taking 5% of the sample at St. Peter specialized hospital. There was close supervision daily.

5.12. Data analysis

Collected data was coded, cleaned, and entered using EPI data version 3.1 and was exported to STATA version 17.0. Descriptive statistical methods were presented using frequency and percentages for categorical variables, medians and IQR for continuous variables. Person-time (incidence density) rate (IR) was calculated for the occurrence of adverse drug events. The Kaplan Meier (KM) curve was used to evaluate survival among predictor variables. Before running the Cox regression model, proportional hazard assumption was checked. Graphical presentation, Schoenfeld residual test and/ or the time-varying Covariates (TVC) were used in the multivariable cox regression for final decision-making, and variables with P-value > 0.05 were considered as fulfilling the

assumption. Variables with a p value below 0.25 in the bivariable Cox regression model were included in a multivariable Cox regression model. Additionally, crude and adjusted hazard ratios with their 95% Confidence Intervals (CI) were estimated, and p-values less than 0.05 indicated statistical significance in the multivariable regression. Model comparison was done using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The smallest AIC was used to choose the best fitting model. The Cox Snell residual was used to check for the goodness of fit.

5.13. Ethical considerations

Anonymity was preserved. Patient names was not used. Each patient had a unique identifier and information was accessed by the principal investigator. Confidentiality was maintained and the records were safely stored in a locked cupboard. The investigator obtained approval from CDT-Africa scientific and ethics review committee to conduct the study. A waiver of informed consent was requested. Written permission to carry out the research was submitted to all selected public hospitals. The principal investigator and the research team only had access to the collected data.

5.14. Dissemination of findings

The results of the study will be presented to CDT Africa, Addis Ababa University, after completion. The results will be published in reputable journals.

6. RESULTS

6.1. Socio-demographic and clinical characteristics

A total of 292 patients were included in the study. Majority of the patients (60.27%) were from St. Peter TB specialized hospital. The median age of patients was 30 (IQR = 29–32). More than half of the patients were male (55.14%), while 45.55% were married. Majority of the patients were from urban areas (82.88%), and only 38.01% had primary education. More than three-fourths (77.05%), of the patients had pulmonary TB, and 59.25% were treated with long term regimen with newer drugs. 96.23% of the patients had RR TB, 22.95% had HIV co-infection, while 15.75% had other comorbidities. Table 1

Table 1 Socio-demographic and clinical characteristics of patients on DRTB treatment in public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023 (N=292)

Variables	N (%)
Age	
1-25	83(28.42)
25-49	157(53.77)
>50	52 (17.81)
Sex	
Male	161 (55.14)
Female	131 (44.86)
Residence	
Urban	242(82.88)
Rural	50(17.12)
Martial status	
Single	130 (44.52)
Married	133 (45.55)
Divorced/Separated	18 (6.16)
Widowed	11 (3.77)
Education	
No formal education	65 (22.26)
Primary education	111 (38.01)
Secondary education	77 (26.37)
Diploma and above	39 (13.36)
BMI	
Severely underweight	89 (30.48)
Underweight	51 (17.47)
Normal	144 (49.32)
Overweight and obese	8 (2.74)

HIV co-infection	
Yes	67 (22.95)
No	225 (77.05)
Other comorbidities	
Yes	46(15.75)
No	246(84.25)
Registration group	
New	132 (45.21)
Relapse	109 (37.33)
Treatment after failure or LTFU	51 (17.47)
Drug susceptibility	
RRTB	281(96.23)
MDR TB	8 (2.74)
Pre XDR TB	3 (1.03)
Concomitant medication use	
Yes	88 (30.14)
No	204 (69.86)
Site of DRTB	
Pulmonary TB	225 (77.05)
Extra pulmonary TB	39 (13.36)
Disseminated TB	28 (9.59)
Treatment regimen	
Long term regimen	31 (10.62)
Long term regimen with new drug	173 (59.25)
Short term regimen	88(30.14)
Patient admission	
Yes	70 (23.97)
No	222 (76.03)
Anemia	
Yes	71 (24.32)
No	221 (75.68)
Treatment completion status	
Good treatment outcome	222 (76.03)
Poor treatment outcome	57 (19.52)
Not evaluated	13 (4.45)

6.2. Incidence and impact of adverse drug reactions

Overall incidence of adverse dug reaction is 8.10 per 100 person-month (PM) (95%CI: 7.02, 9.36) observation. Total follow up time was 2294 months. The overall median survival time was 8 months. The minimum follow-up time was 1 month, while the maximum follow-up time was 27 months. The Kaplan-Meier (KM) curve was used to evaluate survival among predictor variables. Figure 2

A total of 186 (63.69%) DR-TB patients initially free from any adverse drug reaction developed at least one event during treatment**.** The most common adverse drug reaction was GI disturbance (31.85%), followed by peripheral neuropathy (21.92 %), arthralgia (17.47%), visual disturbance (16.44%), and nervous system disorders (8.82%). Less frequently observed ADRs were anemia (4.79%), hearing loss (3.42%), hepatotoxicity (3.08%), prolonged QT interval (1.71%), reaction at injection site (0.68%), nephrotoxicity (0.68%), hypothyroidism (0.34%), increased uric acid (0.34%), and myelosupression (0.34%). Table 2

Drugs identified during treatment were Levofloxacin, Moxifloxacin, Bedaquiline,Linezolid, Clofazamine, Cycloserine, Caperomycin, Proteonamid, pyrazinamide, Ethambutol, Isonaizid, Ethionamide, and Kanamycin. In addition, 17.12% and 21.92% of the patients had temporary and permanent drug discontinuations respectively. Lzd and Cs were the two most common drugs responsible for temporary and permanent drug discontinuation. Serious adverse events occurred in 11.30% of the patients. GI disturbances such as nausea and vomiting and anemia were the most commonly occurring serious adverse events. Lastly, 76.03% of the patients had a good treatment outcome, while 19.52% had poor treatment outcome, and, 4.45% were not evaluated.

Table 2 Characteristics and impact of adverse drug reactions during DRTB treatment in public hospitals in Addis Ababa, Ethiopia from January 2017 to December 2023.(N=292)

ADR	n (%)	Month of presentation (median in month)	Temporary drug discontinuation	Permanent drug discontinuation	RM	DR	SAE n (%)
GI disturbance	93(31.85)						
Nausea and vomiting	81(27.74)	3	1(1.23)	0	6 (7.41)	0	8(9.8)
Epigastric pain	16(5.48)	4	0	0	0	0	0
Abdominal pain	3(1.03)	3	0	0	0	0	0
Peripheral	64(21.92)	10	12(18.75)	19(29.69)	0	5(7.81)	0
Arthralgia	51(17.47)	6	6(11.76)	6(11.76)	0	3(5.88)	0
Visual disturbance	48(16.44)	7.5	19(39.58)	24(50)	0	0	0
Nervous system disorders	24(8.82)						
Hallucination	9 (3.08)	3	4(44.44)	2 (22.22)	0	2 (22.22)	3 (33.3)
Depression	4 (1.37)	5.5	1(25)	0	0	1 (25)	0
Insomnia	13 (4.45)	6	1(7.69)	2(15.38)	0	0	0
Suicidal attempts	2 (0.68)	9.5	0	2 (100)	0	0	0
Anemia	14(4.79)	7	5(35.71)	5(35.71)	0	3 (21.43)	12 (85.7)
Hearing loss	10(3.42)	3	0	8(80)	0	0	3(30)
Hepatotoxicity	9(3.08)	2	6(66.7)	1 (11.1)	1 (11.11)	0	6 (66.6)
Prolonged QT interval	5(1.71)	3	1(20)	2(40)	0	1 (20)	0
Reaction at injection site	2(0.68)	3.5	0	0	0	0	0
Nephrotoxicity	2(0.68)	2	0	2 (100)	0	0	1(50)
Hypothyroidis m	1(0.34)	6	0	0	0	0	0
Increased uric acid	1(0.34)	7	1(100)	0	0	0	0
Myelosuppresio n	1(0.34)	7	0	1(100)	0	0	1 (100)

Abbreviations; RM : Regimen modification, SAE : Serious adverse event, DR : Dose reduction

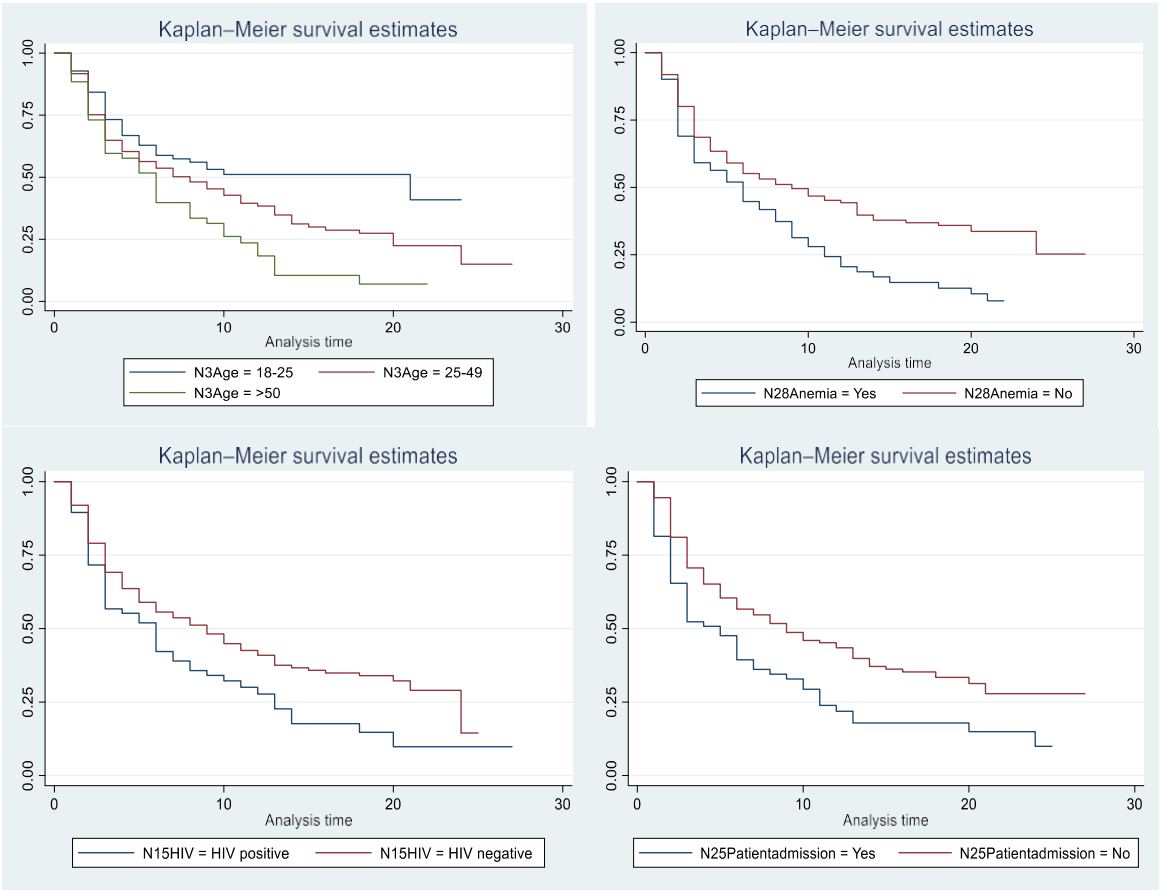

Figure 6 Kaplan-Meier survival curve among DRTB patients in selected public hospitals in Addis Ababa, Ethiopia, from 2017- 2023 for age, anemia at presentation ,HIV, and patient admission (hospitalization).

6.3. Predictors of adverse drug reactions

In order to identify predictors of adverse drug reactions, Cox proportional regression model was used. Before fitting the covariate into the model, the proportional hazard assumption was checked graphically, using the schoenfeld test and or using TVC. Bivariate analysis showed that age, HIV co-infection, concomitant medication use, registration group, regimen, patient admission (hospitalization), treatment completion status, and anemia were associated with adverse drug reactions. (Table 3) In the multivariable Cox regression, three variables were significantly associated with adverse drug reaction. Patients age older than 50 years (AHR = 1.87, 95%CI: 1.19-2.93), patient admission status (AHR = 1.53, 95%CI: 1.10-2.13) and anemia at presentation (AHR = 1.58, 95%CI: 1.16-2.17) were statistically significant predictors of adverse drug reactions. Accordingly, patients in the age group of 25-49 had a 53% increased risk of experiencing ADRs, while patients older than 50 years had an 87% increased risk of experiencing adverse drug reactions compared to those below 25 years of age. Patients with anemia at presentation were 58% more likely to encounter ADRs compared to non anemic ones. Additionally, hospitalized patients were 53% more likely to have an ADRs compared to those on clinic based ambulatory care. (Table 4)

Table 3 Bivariate analysis of factors associated with occurrence of adverse drug reactions during DRTB treatment in public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023.(N=292)

Variables	ADR		CHR(95% CI)	P value
	Event (186)	Censored (106)		
Age				
1 -25	39	44	1	
25-49	103	54	1.49(1.03,2.16)	0.032
>50	44	8	2.20(1.43,3.40)	0.000
Sex				
Male	105	56	1	
Female	81	50	0.92(0.69, 1.23)	0.588
Residence				
Urban	154	88	1	
Rural	32	18	1.04(0.71, 1.52)	0.826
Martial status				
Widowed	7	4	1	
Single	78	52	0.94(0.43, 2.05)	0.889
Married	85	48	1.01(0.46, 2.19)	0.968
Divorced/separated	16	2	1.57(0.64, 3.82)	0.320
Education				
No formal education	42	23	1	
Primary education	69	42	1.03(0.70, 1.51)	0.874
Secondary education	52	25	1.10(0.73, 1.66)	0.638
Diploma and above	23	16	1.00(0.60, 1.67)	0.991
BMI				
Severely underweight	57	32	1	
Underweight	30	21	0.78(0.50, 1.22)	0.292
Normal	94	50	0.88(0.63, 1.22)	0.454
Overweight and obese	5	3	1.24(0.49, 3.11)	0.635
HIV co-infection				
No	134	91	1	
Yes	52	15	1.472(1.06, 2.03)	0.018
Other comorbidities				
No	152	94	1	
Yes	34	12	1.21(0.83, 1.76)	0.299
Registration group				
New	87	45	1	
Relapse	73	36	1.04(0.76, 1.43)	0.763
Treatment after failure or Treatment after LTFU	26	25	0.64(0.41, 0.99)	0.048

Drug susceptibility				
RRTB	178	103	1	
MDR TB	7	1	1.52(0.71,3.25)	0.272
Pre XDR TB	1	2	0.60(0.08,4.32)	0.617
Concomitant medication use				
No	119	85	1	
Yes	67	21	1.45(1.08,1.97)	0.014
Site of DRTB				
Disseminated TB	19	9	1	
pulmonary TB	142	83	1.11(0.68,1.80)	0.660
Extra pulmonary TB	25	14	1.07(0.59,1.96)	0.808
Treatment regimen				
Short term regimen	40	48	1	
Long term regimen	23	8	1.38(0.82,2.32)	0.221
Long term regimen with new drug	123	50	1.34(0.93,1.93)	0.113
Patient admission				
No	131	91	1	
Yes	55	15	1.64(1.20,2.26)	0.002
Anemia				
No	126	95	1	
Yes	60	11	1.65(1.21,2.25)	0.001
Treatment outcome				
Good treatment outcome	142	80	1	
Poor treatment outcome	38	19	1.28(0.89,1.84)	0.173
Not evaluated	6	7	1.18(0.52,2.70)	0.678

Abbreviations: CHR: Crude hazard Ratio, CI: Confidence Interval,

Table 4 Multivariate analysis of factors associated with occurrence of adverse drug reactions during DRTB treatment in public hospitals in Addis Ababa, Ethiopia, from 2017 to 2023.(N=292)

Variables	ADRs		AHR(95% CI)	P value
	Event (186)	Censored (106)		
Age				
1 -25	39	44	1	
25-49	103	54	1.53(1.05,2.21)	0.023
>50	44	8	1.87(1.19,2.93)	0.006
HIV status				
Negative	134	91	1	
Positive	52	15	1.12(0.79, 1.58)	0.506
Registration group				
New	87	45	1	
Relapse	73	36	0.98(0.71, 1.34)	0.909
Treatment after failure or Treatment after LTFU	26	25	0.64(0.41, 0.99)	0.049
Concomitant medication use				
No	119	85	1	
Yes	67	21	0.96(0.63,1.47)	0.866
Treatment regimen				
Short term regimen	40	48	1	
Long term regimen	23	8	1.26(0.75,2.13)	0.374
Long term regimen with new drug	123	50	1.09(0.75,1.60)	0.624
Patient admission				
No	131	91	1	
Yes	55	15	1.53(1.10,2.13)	0.011
Anemia				
No	126	95	1	
Yes	60	11	1.58(1.16,2.17)	0.004
Treatment outcome				
Good treatment outcome	142	80	1	
Poor treatment outcome	38	19	1.06(0.72,1.57)	0.739
Not evaluated	6	7	1.24(0.53,2.90)	0.608

Abbreviations: AHR: Adjusted hazard Ratio, CI: Confidence Interval

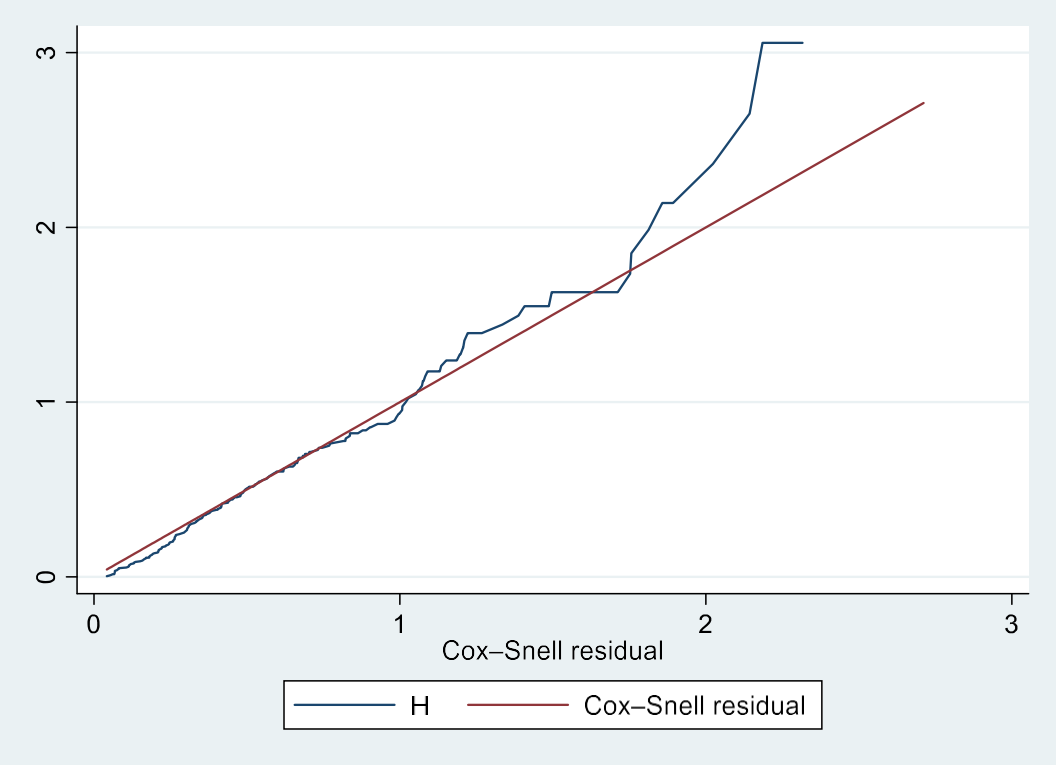

Figure 7. Cox-snell residual result

7. DISCUSSION

DR TB is a major public health threat resulting in significant morbidity and mortality, and its treatment is challenging due to the occurrence of ADRs. In this study, the incidence of ADR was 8.10 per 100 person month observation. This result is slightly comparable with studies done in Ethiopia and Uganda, which had an incidence of 5.79 and 5.56 per 100 PM observation, respectively. (14) (17) However, it is much lower than a study in Georgia, which had an incidence of 1.16 per 100 PM observation. (58) There is variation between these studies due to differences in the definition of a specific adverse drug reaction, differences in the type of adverse event included (such as severe or non-severe, symptomatic or laboratory-confirmed) and variations in the type of regimen used during treatment.

GI disturbance is the most common ADR occurring in almost one third of the participants (31.85%). This result is comparable with studies done in India and Vietnam, occurring in 34.42% and 38.5% of the patients, respectively. (59) (60) However, our result is lower than previous studies done in Ethiopia (70%), and China (65.4%), but higher than a study done in South Korea (18.4%). (35) (18) (61) The variation between the results could be due to the difference in the minimum follow up time, GI disturbance definition, type, and profession of health workers giving care at clinics, monitoring, and follow-up mechanisms of treatment centers. Subgroup disturbances in our study included nausea and vomiting (27.74%), abdominal pain (1.03%), and epigastric pain (5.48%). Nausea and vomiting was severe enough to cause serious adverse events in 9.8% of the patients, while 7.4% had regimen modifications.

Peripheral neuropathy occurred in 21.92% of the patients, which is much higher than a study in Ethiopia, which was seen in 9.14% of the patients, but the regimen in this study didn't include new and repurposed second line drugs such as Lzd, which could have contributed to the lower rate of peripheral neuropathy. (14) Furthermore temporary and permanent drug discontinuation occurred in 18.75% and 29.69% of the patients, respectively. Arthralgia was the 3rd most common ADR, occurring in 17.47% of the patients comparable with studies done in India (14.38%). (38) However, lower than reported in other studies. (16, 35) In our study, temporary and permanent drug discontinuation

occurred in 11.76%, while dose reduction was seen in in 3(5.8%) patients, with no serious adverse event. Only one patient with arthralgia had increased uric acid levels.

Visual disturbances occurred in 16.44% of the patients, resulting in temporary and permanent drug discontinuation in 39.58% and 50%, respectively. This result is consistent with a study done in western India in which visual changes occurred in 16% of the patients. (62) Even though E, H, Lzd, S and fluoroquinolones have been associated with optic neuropathy; Lzd and E were the main culprit drugs in our study. (5, 63) Psychiatric disorders were found in 8.82% of the patients, in line with studies done in Indonesia (7.5%) and China (9.28%). (64) (65) However, it is lower than a 2019 study done in Ethiopia (15.32%) and Vietnam (33.75%). (14) (60) This can be due to differences in the definition of psychiatric disorders and discrepancies between studies on the number of patients on Cs containing regimen. The most common psychiatric disorder in our study was insomnia (4.45%), followed by hallucinations (3.08%), depression (1.37%), and suicidal attempts in 2 patients (0.68%). Cs was responsible for all psychiatric disorders and was permanently discontinued in 6 patients, and hallucinations caused serious adverse event in 3 patients.

In this study, hematologic abnormalities such as anemia and myelosuprresion occurred in 4.79% and 0.34% of the patients, respectively, but were serious adverse drug reactions resulting in life-threatening conditions and prolonged hospitalization, with LZD being the suspected drug. Even though prolonged LZD use has been associated with hematologic abnormalities, it is highly dependent on the dose, duration of use and is reversible with appropriate treatment.

Hearing loss occurred in 3.42% of the patients, and of these, 3 (30%) had serious adverse events that resulted in permanent disability. The prevalence of ototoxicty was higher in studies in Italy (11.5), Uganda (9%), and Pakistan (11.2%). (43, 49) (66) This can be due to the routine use of injectable aminoglycosides in the above studies, and the absence of routine audiometric evaluation during treatment in the Ethiopian context could have contributed to the lower rate of ADRs.

Additionally, 3.08% of the patients had hepatotoxicity comparable with studies done in Vietnam (5.8%) and India (1.6%). (59) (60) Of those patients with hepatotoxicity, temporary drug discontinuation, permanent drug discontinuation, and Serious adverse

events occurred in 66.7%, 11.1%, and 66.6% respectively. Prolonged QT interval was seen in 5 (1.71%) of the patients, while temporary and permanent drug discontinuation occurred in 1 (20%) and 2 (40%) of the patients, respectively. This result is comparable to a study done in Uganda (2.9%), but much lower than a study in Ethiopia (16.7%), which showed preliminary results primarily focusing on patients only on Bdq and Dlm containing regimens. (18) (67) Nephrotoxicity occurred in 2 (0.68%) patients on whom the drug was permanently discontinued and the other needed prolonged hospitalization. This result is much lower than another study done in Ethiopia, in which nephrotoxicity was found in 6.7% of the patients, but this study predominantly included patients who are on aminoglycoside-containing regimens, which could have contributed to the higher prevalence of nephrotoxicity. (22)

In the multivariable regression, age, anemia, and patient admission or hospitalization were predictors of adverse drug reaction. Adverse drug reactions occurred more frequently in the older age group of 25-49 and > 50. This result is in line with studies done in Ethiopia, Iran, and Pakistan. (14) (15) (49) As age increases, there are changes in drug pharmacokinetics and pharmacodynamics such as alteration in the hepatic blood flow distribution, which commonly affects liver function, and combined with a reduced renal function, the clearance rate of metabolized drugs is reduced . Additionally, since the older age groups have a higher prevalence of chronic diseases, they are more likely to take multiple drugs simultaneously, increasing the risk of adverse drug reactions. (39, 68)

Anemia is another predictor of occurrence ADRs in DRTB patients. Anemic patients at presentation were 58% more likely to develop adverse drug reactions compared to non-anemic ones. This is in line with studies done in Ethiopia and Peru. (14) (40) Anemia is one of the most common laboratory abnormalities present in TB, occurring due to nutritional deficiency, malabsorption, and chronic inflammation. (69) Furthermore, other studies have also shown that the presence of anemia shows severity of the disease, with a potential to affect subsequent treatment outcomes and increase the risk of recurrent TB infection. (70) On the other hand, many of the medications such as H, Cs, E, Z, Cfz, Lfx, and Lzd used for DRTB can also cause hematologic adverse drug reactions, including anemia.(71)

Patient admission status or hospitalization is another factor associated with occurrence of adverse drug reaction. Admitted patients were 53% more likely to develop adverse drug reactions compared to those on ambulatory care. Since MDR-TB patients could be effectively treated on an ambulatory basis, clinic–based Ambulatory mode is the main model of care, and hospitalization is reserved for patients with severe medical or social justification. Admitted patients usually have a more severe disease and are more at risk for greater number of ADRs. (5) Additionally Hospitalized patients usually receive close and frequent follow up during treatment, which can lead to increased reporting of adverse drug reactions among both health care professionals and patients.

There have been contradictory results regarding the association between ADRs and treatment outcomes. (38) (56) Our study demonstrated that ADRs weren't associated with treatment outcomes. This is in line with studies done in Italy, Malaysia, and Pakistan which have shown no association between the development of ADRs and treatment outcomes. (29) (66) (72) Additionally, despite the high incidence of ADR in our study, 76.03% of the patients had good treatment outcome, suggesting the occurrence of ADRs doesn't necessarily result in poor treatment outcomes.

8. STRENGTH AND LIMITATION OF THE STUDY

This is a study done after the introduction of new and repurposed drugs and sheds light on the trends, timings, clinical outcomes, and impacts of ADRs during treatment. Furthermore, by identifying factors associated with ADRs, it could allow health care workers to appropriately risk-stratify patients for closer management and improve outcomes. However, there are a few limitations to our study. Since it is a retrospective study based on a review of the patient charts, collected data solely depends on available recordings on the patient charts, which has made it difficult to grade ADRs and made follow up laboratory investigations incomplete. Moreover, there can be an underestimation or overestimation of reported ADRs depending on detecting and documenting ability of the treating physician. Additionally, ADRs such as hearing loss and visual disturbance were not routinely assessed using objective methods and were dependent on the clinical presentation for diagnosis due to limited resources. Lastly, the final outcome of transferred-out patients and the long term sequel of certain ADRs were not available.

9. CONCLUSION AND RECOMMENDATIONS

More than half of the participants had experienced at least one ADR. Older age, patient admission, and baseline anemia were all independently associated with ADRs during MDR TB treatment. GI disturbance, followed by peripheral neuropathy and arthralgia, were the most commonly occurring ADRs during treatment. Additionally, nausea and vomiting were the major causes of regimen modification, while LZD and Cs were the two most common drugs that resulted in temporary and permanent drug discontinuation.

The incidence of ADR was high in this study. Special attention should be given to susceptible groups of older age, hospitalized patients, and anemic patients on baseline for early prediction, timely management, and appropriate formulation of treatment regimens by considering ADRs. Additionally, close monitoring of ADRs at specific timings in preparation for higher center care can have a critical impact on improving treatment outcome.

ADRs such as nausea and vomiting, specific drugs such as Lzd, Cs and aminoglycosides were major cause of regimen modification, drug discontinuation, and permanent disability and hence need close monitoring and follow up.

Future studies should further explore the long term sequel of ADRs such as peripheral neuropathy, visual disturbances, and hearing loss. Additionally, focus on specific ADRs and predicting factors with a prospective method can be essential to better understand the occurrence of ADRs and further improve MDR TB treatment care.

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11. ANNEXES

Annex 1: Data collection tools

Instructions

1. This data collection format is prepared to use in collecting data for the assessment of ADRs of DR TB patients on treatment.
2. It has three parts. Part one contains sociodemographic and behavioral characterstics, while part two and three contains clinical and ADR information respectively.
3. Please read carefully and try to fill the requested data from the patient register Part-1 Participant Socio-demographic and behavioral information

Number	Variable	Data
1.1	Facility name	
1.2	Participant ID	
1.3	Age	
1.4	Sex	1- Male
		2- Female
1.5	Marital Status	1- Single
		2- Married
		3- Widowed
		4- Divorced
1.6	Highest educational Level completed	1- Elementary and middle School(Grade 1-8)
		2- High School (Grade 9-12)
		3- Diploma
		4- BSC degree or more (college or university)
		5- No formal Education
1.7	Area of Residence (Write the name of area of residence)	1.Urban 2.Rural
1.8	Religion	1- Muslim
		2- Orthodox Christian
		3- Protestant
		4- Catholic Christian
		5- Jehovah's Witness
		6- Atheist
		7- Others
1.9	Estimated average monthly income in birr	

1.10	History of smoking cigarette	1.yes If no skip to question no 1.11 2.no
1.11	Smoking during treatment	1.yes 2.no
1.12	History of drinking alcohol	1.yes 2.no
1.13	History of chewing chat	1.yes 2.no
1.14	History of substance abuse	1.yes 2.no

Part -2 Clinical information

Number	Question	Answer
2.1	Weight	
2.2	Height	
2.3	BMI	
2.4	HIV status of the patient	1. Positive 2. Negative
2.5	Comorbidity other than HIV	1.yes 2.no if yes please specify
2.6	Any medication the patient has taken other than anti-DR-TB drugs	1. yes 2.no
2.7	Registration group	1. New 2. Relapse 3. Treatment after failure 4. Treatment after LTFU 5. Others
2.8	Result of drug susceptibility testing (number and specific drugs for which the bacilli is resistant)	Please specify
2.9	Site of DR TB infection	1. Pulmonary 2. Extrapulmonary 3. Diseminated
2.10	Date of DR TB drugs initiation	Please specify
2.11	Date of end of treatment	Please specify
2.12	Regimen during treatment	Please specify
	Patient admitted	1. Yes 2. No
2.13	Completion status of DR TB treatment	1.Good treatment outcome 2.Adverse treatment outcome 3.Others

	Baseline laboratory result		
2.14	CBC	WBC	(x 10^3/l)
		Hb	(g/dl)
		PLT	(x 10^3/l)
2.15	LFT	ALT	(U/l)
		AST	(U/l)
		ALP	(U/l)
		BILRUBIN	_____(µmol/l)
2.16	RFT	Cr	_____(mg/dl)
		Urea	_____(mg/dl)
2.17	TFT	T3	(nmol/l)
		T4	_____(nmol/l)
		TSH	(µU/l)
2.18	Electrolyte	K+	_(mmol/l)
2.19	Hearing loss at initiation of treatment		1.Yes 2.No
2.20	Presence of visual impairment		1.Yes 2.No
2.21	Documented QT prolongation		1.Yes 2.No
2.22	Does the patient have an ADR?		1.Yes 2.No
2.23	Frequency of ADRs ?		Please specify

Part 3. Adverse drug reaction

Conventional codes *(Check the codes and fill the blanks)*		
Consequence of the ADR(seriousness)	**Intervention done for the ADR**	
1 = Resolved without sequel 2 = Death 3 = Life threatening condition 4 = Requires or prolongs hospitalization 5 = Disability or permanent damage 6 = Congenital anomaly/ birth defect 7 = No information	1= No intervention 2 = Dose reduction 3 = Temporary drug discontinuation 4= Permanent drug discontinuation 5 = Regimen Modification 6 = Drug to treat ADR 7 = No information 8 = Other ___	WHO-UMC Causality term 1.Certain 2.Probable 3. Possible

	ADRs	Yes √ No x	Date	Seriousness	Intervention	Causality Term
3.1	GI disturbance					
	Nausea, vomiting					
	Diarrhoea					
	Abdominal pain					
	Anorexia					
	Reflux hematemesis					
	Positive occult blood on stool					
	Heartburn					
	Epigastric pain					
	Results gastroscopy (specify results)					
3.2	Hepatotoxicity					
3.3	Seizures, epilepsy					
3.4	Psychosis					
	Hallucinations, auditory hallucinations					
	Confusing thoughts					
	Depression					
	Insomnia					
	Losing focus					

	Having suicidal					
3.5	Peripheral neuropathy					
	Numbness and tingling on extremities					
	Diminished or absent reflexes					
	Diagnosed with nerve conduction tests					
3.6	Arthralgia					
3.7	Allergic reaction					
	Rash					
	Itchy					
	Hypersensitive skin with light					
	ADRs	**Yes √ No x**	**Date**	**Seriousness**	**Treatment**	**causality**
3.8	Nephrotoxic					
3.9	Vestibular - auditory disorders					
	Blurred hearing/ deaf					
	Vertigo					
3.10	Visual disturbances					
	Blurred vision					
	Difficulty in distinguishing colors					
3.11	Hypothyroidism					
3.12	Decreased potassium					
3.13	Increased Uric acid					
3.14	CBC					

	Hemoglobin					
3.15	Reactions at the injection site					
	Pain					
	Swollen					
	Callosity					
	Itchy					
3.16	Anaphylaxis					
	On skin (rash,itchy and vasodilation...)					
	On répiratory (Dyspnea, tracheal constriction...)					
	Hypotension					
	On gastrointestinal (stomach cramps, diarrhea					
3.17	Other					