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**ORIGINAL ARTICLE**

# SEVERE ADVERSE EFFECTS ASSOCIATED WITH MULTIDRUG RESISTANT TUBERCULOSIS MEDICATIONS AMONG PATIENTS ATTENDING ALERT HOSPITAL, ETHIOPIA.

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## ABSTRACT

***Background:*** *Ethiopia is one of the countries with high Multidrug - Resistant Tuberculosis (MDR-TB) burden. According to the national sentinel drug resistance survey conducted in 2012-2014, 2.3% of new TB cases and 17.8% of previously treated TB cases were estimated to have MDR-TB in Ethiopia. MDR-TB medications have severe adverse effects. Little is known about the adverse effects of MDR-TB medications in Ethiopia. Therefore this study was aimed at determining the incidence of severe adverse effects associated with MDR-TB therapy.*
***Methods:*** *A cross-sectional study design using a retrospective medical record review of 238 patients with Drug-Resistant Tuberculosis was conducted to assess severe adverse effects of MDR-TB therapy and associated factors. Applying multiple logistic regression models, adjusted odds ratio and their 95% confidence intervals were used to identify important risk factors associated with treatment adverse effects.*
***Results:*** *One or more adverse effects developed in 219 cases (92 %). Severe adverse effects, which led clinicians to suspend one or more drugs from the treatment regimen was seen in 46 cases (19.3%). Adverse effects observed most frequently include: Gastrointestinal Effect (73.1%), Hypokalemia (45.4%), Arthralgia (29.4%), Sleep Disturbance (12.6%), Psychiatric Problems (7.2%), Hypothyroidism (5.9%), Renal Toxicity (5%), Neuropathy (3.4%), and Hepatotoxicity (0.8%). Co-morbid conditions of HIV/AIDS and Diabetes Mellitus, Older age, and Homelessness were identified as important predictors of severe adverse effects.*
***Conclusion:*** *Severe adverse reactions to MDR-TB therapy were common and resulted in the suspension of one or more drugs in the regimen. In spite of the severe adverse effects, we suggest that efforts should be made to continue treatment by modifying the treatment regimen. All diagnostic tests and ancillary medications need to be always available for early detection, treatment, and follow up of adverse events. Special attention should be given for elderly, homeless, HIV/MDR-TB, and Diabetes/MDR-TB co - infected patients.*
***Key words****: Severe Adverse Effect, MDR-TB therapy, ALERT Hospital, Ethiopia*

## INTRODUCTION

Ethiopia is one of the countries with high multidrug resistant tuberculosis burden. According to the recent national sentinel drug resistance survey conducted in 2012-2014, 2.3% of new TB cases and 17.8% of previously treated TB cases were estimated to have MDR in Ethiopia. In Ethiopia, starting from the introduction of second line drugs (SLD) up to 2014/2015(EFY, 2007), a cumulative number of 2,156 MDR TB patients were enrolled in SLD treatment and 597 MDR TB patients were enrolled in SLD treatment in 2014/2015 (Ethiopian Fiscal Year, EFY 2007) only (1).

Poor treatment outcomes, longer treatment duration (about two years), higher treatment costs, and many more complications make MDR-TB a more complex disease than TB (2-3).

Long-term use of multidrug regimens has raised concern over the possibility of sever adverse effects among patients being treated. The severe adverse reactions to anti-tuberculosis drugs can cause significant morbidity and mortality by compromising treatment regimens for MDR -TB. There exists a large literature on adverse effects of drug resistant tuberculosis medications. In these studies, adverse effects were recorded for 69.2% to 80.6% of the cases. Moreover, suspension of drug was recorded in 20 to 55.5 % of the cases (4-10). The most frequently mentioned adverse effects in these studies were gastrointestinal effect, peripheral neuropathy , hearing loss, psychiatric episodes, hepatitis and renal failure.

A systematic review and meta-analysis of 26 articles in China described that 373 patients developed liver injury (11). Similarly, a systematic review of 21 Iranian articles showed 33.63% of patients developed an adverse reaction in 7 studies.

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In the same review, hepatitis (2.5 - 45.3%) was reported in nearly all of the studies (12).

Adverse effects were significantly more common in patients with HIV co-morbidity, older age, females, longer duration of hospitalization, alcoholism, smoking, concomitant drug intake, and low hemoglobin level at base line (4, 7, 12, 13, and 14).

In Ethiopia, severe adverse drug effects associated with the treatment of MDR-TB have not been well studied. We found only one similar study conducted in Addis Ababa (14). In this study, any episodes of adverse effects were described regardless of whether it resulted in suspension of drug or not.

Anti-TB drug adverse effects are integral risks for patients under any type of anti-TB therapy, especially drug-resistant cases. However, emergence of adverse effects may depend on patients' characteristics but also on associated events during therapy. This might determine adherence and therefore, therapy success. The problem of adverse effects from anti-TB drugs in case of MDR-TB has two major aspects. One is the patient's direct risk of developing severe life-threatening complications. Such complications can easily be reduced if patients at risk are monitored in an appropriate manner. The other side of the problem, which has not been addressed in studies so far, is that adverse effects may lead clinicians to suspension and or withdrawal of one or more of the basic drugs. Moreover, there is limited evidence about the problem in the Ethiopian setup. Thus, we wanted to determine the occurrence of severe adverse effects associated with MDR-TB treatment. We further sought to determine whether existing clinical strategies would permit, under local TB program conditions, the management of adverse effects without requiring the discontinuation of MDR-TB therapy. The study finding could assist to improve the effectiveness of individualized MDR-TB treatment regimen and in the planning of national MDR-TB treatment strategies.

## MATERIALS AND METHODS

All Africa Leprosy Rehabilitation and Training Center (ALERT) was selected as the study site due to the fact that it serves Addis Ababa city, and some other regions that do not have their own MDR-TB treatment initiation and follow up center. The center has a comprehensive TB unit to initiate treatment and follow-up of patients with MDR-TB. The unit provides long-term hospitalization, with all required drug therapies free of charge to the recipient.

We employed a cross sectional study using retrospective medical record review of drug-resistant tuberculosis patients; aged greater than 15 years and resistant to at least one 1$^{st}$ line anti TB-drug at ALERT Hospital in January 2015. We reviewed all medical records of these cases available at the medical record room during the data collection period. Sample size was determined using single population proportion formula. In this regard, a population proportion of 20 % was used from a previous study conducted in Northern Lima; in this study one or more anti TB drugs were suspended in 20% of patients (15). Using 95% confidence level and 5% degree of precision, the required number of samples was 246.

The outcome variable for this study was severe adverse effect, which was operationally defined as any undesirable or harmful effect associated with the administration of drugs to treat MDR-TB and resulted in suspension or withdrawal of one or more second line anti TB drugs. The word “suspend” was used for the temporary discontinuation of one or more drugs, while “withdrawal” was used for permanent discontinuation. Sex, age, previous history of TB, site of TB, type of drug resistance, homelessness, high-risk drinking (for women, high-risk drinking is defined as more than 3 drinks on any single day and more than 7 drinks per week. For men, it is defined as more than 4 drinks on any single day and more than 14 drinks per week), cigarette smoking, status of HIV/AIDS, and diabetes mellitus co-morbidity were considered independent variables. A structured data compilation form was used to extract data from patients’ medical records (registration book, patients’ card, and follow up sheet). The data were collected by trained nurses working in ALERT Hospital MDR-TB clinic. Data entry into the computer was done using EPI Info version 3.5.4 and data entered were then transferred to the Statistical Package for Social Sciences (SPSS) version 20 for analysis. Binary Logistic Regression was the main statistical method applied and both Bivariate and Multivariate analyses were considered. The unadjusted (crude) and adjusted Odds ratios together with their corresponding 95% confidence intervals were computed. P-value $\leq 0.05$ was considered statistically significant in this study.

The research protocol was approved for ethical issue by the Armauer Hansen Research Institute (AHRI)/ALERT institutional review board (Protocol No. P040/14). Individual records were coded and accessed only by the research staff. In addition, personal identifiers were removed from data collection tools.

The recorded data were kept in a secured place with strict confidentiality. Informed consent was waived because of the use of secondary data.

## RESULTS

A total of 250 patient files were reviewed, of which 238 were eligible for inclusion in the study. The study sample comprised 104 females and 134 males, with a mean age of 32.7 years; ranging from 15 to 64 years and the median duration of therapy at the time of analysis was 9.6 (range, 1 –24.33) months. The median initial weight for these patients was 48 (range, 30 – 78) kg.

Regarding registration, 8.8 % (21) patients were registered as new cases; the remaining 91.2% were registered with a history of first line anti TB treatment; 49.2%, 29.4%, 8.8%, and 3.8% were registered after the failure of retreatment, after the failure of first line treatment, after relapse, and after a loss to follow up respectively. Among the cases, 93.7 % were pulmonary tuberculosis patients. Six patients did not have a formal living home. 54 (22.7%) patients had high-risk drinking and/ or smoking habit.

Sixty-One (25.6%) of them had one or more co-morbid conditions at the time of enrollment in individualized MDR-TB therapy. HIV/AIDS was the most frequent baseline finding occurring in 13.4% of the patients; twenty-eight (85.5%) were concomitantly on highly active anti retroviral Therapy (HAART) and multidrug-resistant tuberculosis treatment.

Other co-morbid conditions at MDR-TB diagnosis included psychiatric disorders 10(4.2%), diabetes mellitus 7 (2.9 %), seizure disorders 4(1.7%), renal insufficiency 3(1.3%), anemia 3(1.3%), and chronic liver disease 2(0.8%).

Treatment regimens included a mean of 5.3 (5 –7) drugs. At least one parenteral drug was administered in all of the cases. The most common drug regimen prescribed for 137(57.5%) cases at enrolment was a combination of Pyrazinamide(Z), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserin (Cs), and Capreomycin (Cm). The second most frequently used drug regimen at enrolment was a combination of Pyrazinamide (Z), Ethambutol (E), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserin (Cs), and Capreomycin (Cm); which was prescribed for 57 (23.9%) cases.

One or more adverse effects developed in 92% (219) cases. These effects led clinicians to suspend one or more drugs from the treatment regimen in 46 cases (19.3%). All anti-TB drugs were discontinued in 7 cases for a mean duration of 6.28 days. Cysloserine (Cs) was discontinued in 10 cases for a mean duration of 11.25 days. Capromycin (Cm) was discontinued in 25 cases for a mean duration of 8.9 days. Kanamycin (Km) was discontinued in 3 cases for a one - week duration. Ethionamide (Eto) and para-aminocylicylic acid (PAS) were discontinued for one patient for 1 week.

Adverse effects observed most frequently were gastrointestinal effect (73.1%), hypokalemia (45.4%), arthralgia (29.4%), sleep disturbance (12.6%), psychiatric problems (7.2%), hypothyroidism (5.9%), renal toxicity (5%), neuropathy (3.4%), and hepatotoxicity (0.8%) (Table 1).

**Table 1:** The frequency of all adverse effects reported among patients, who were treated for MDR-TB at ALERT Hospital, Ethiopia up to January, 2015. n = 238.

| **Adverse effect** | | **Count** | **Percentage (%)** |
|---|---|---|---|
| Gastrointestinal Effect | Yes | 174 | 73.1 |
| | No | 64 | 26.9 |
| Hypokalemia | Yes | 108 | 45.4 |
| | No | 130 | 54.6 |
| Arthralgia | Yes | 70 | 29.4 |
| | No | 168 | 70.6 |
| Sleep disturbance | Yes | 30 | 12.6 |
| | No | 208 | 87.4 |
| Psychiatric Problems | Yes | 17 | 7.2 |
| | No | 221 | 92.8 |
| Hypothyroidism | Yes | 14 | 5.9 |
| | No | 224 | 94.1 |
| Renal Toxicity | Yes | 12 | 5 |
| | No | 226 | 95 |
| Neuropathy | Yes | 8 | 3.4 |
| | No | 230 | 96.6 |
| Hepatotoxicity | Yes | 2 | 0.8 |
| | No | 236 | 99.2 |

***Treatment outcome***

At the time of analysis treatment outcome was registered for 79(33.2%) cases, and the other 159 (66.8%) cases remained on treatment at the time of analysis, thus, their treatment outcome is not given. Of those whose treatment outcome was registered, treatment was favorable in 49 (62%) of 79 cases, including cure in 26 cases (33%) and treatment completed in 23 cases (29.1%). Thirty cases (38%) had unfavorable outcomes due to death (14 cases, 17.7%), treatment failure (6 cases, 7.5%) and defaulters in (10 cases, 12.6%).

***Predictors of Severe Adverse Effect***

As can be noted from the findings of the bivariate analyses (Table 2) four of the ten variables showed a significant association with the occurrence of severe adverse effect (SAE) at a 5% level of significance. In this regard, age group, homelessness, co-morbidity with HIV/AIDS, and diabetes mellitus showed significant association with the occurrence severe adverse effect.

The multivariate logistic regression analysis (Table 2) which controls for the undesirable effects of confounding variables was used by taking all the 10 predictor variables into account simultaneously. Similar to the Bivariate analysis; age group, homelessness, and co-morbidity with HIV/AIDS and diabetes mellitus showed significant association with severe adverse effect.

**Table 2.** Factors associated with sever adverse effects (SAE) of second line anti-TB drugs used to treat MDR-TB patients at ALERT Hospital, Ethiopia up to Januar 2015. n=238

| **Variables** | **Category** | With SAE | Without SAE | **COR** | **AOR** | **95% CI for AOR** |
|---|---|---|---|---|---|---|
| Sex | Male | 25 | 109 | 1 | | |
| | Female | 21 | 83 | 1.103 | | |
| Age | 15-44 | 36 | 171 | 1 | 1 | |
| | 45-64 | 10 | 21 | 2.26* | 2.65* | 1.01-6.95 |
| Previous History of TB | Yes | 40 | 177 | 1.21 | | |
| | No | 6 | 15 | 1 | | |
| Site of TB | Pulmonary | 43 | 180 | 1 | | |
| | Extrapulmonary | 3 | 12 | 1.04 | | |
| Type of DR | Mono | 9 | 37 | 1 | | |
| | MDR | 37 | 155 | 0.98 | | |
| Homelessness | Yes | 4 | 2 | 9.04 * | 10.01* | 1.37-73.95 |
| | No | 42 | 190 | 1 | | |
| High – Risk drinking | Yes | 7 | 22 | 1.38 | | |
| | No | 39 | 190 | 1 | | |
| Smoking | Yes | 6 | 19 | 1.36 | | |
| | No | 40 | 173 | 1 | | |
| HIV/AIDS | Positive | 15 | 17 | 4.98* | 4.90* | 2.01-11.96 |
| | Negative | 31 | 175 | 1 | 1 | |
| DM | Yes | 5 | 2 | 11.58* | 7.65* | 1.15-50.62 |
| | No | 41 | 190 | 1 | 1 | |

In this regard, older age groups were 2.65 times more likely to develop severe adverse effects compared to younger age groups (AOR=2.65, 95% CI = 1.01-6.95). Patients who do not have a formal living home were 10.01 times more likely to develop severe adverse effect (AOR=10.01, 95%CI = 1.37-73.95).

With regard to co-morbid conditions, MDR-TB patients who had a concomitant infection with HIV/AIDS and diabetes mellitus had high risk for severe adverse effects associated with MDR-TB therapy. In this regard, HIV-MDR/TB patients were 4.90 times more likely to develop severe adverse effects during MDR-TB treatment compared to HIV negative patients (AOR = 4.90, 95% CI = 2.00-11.96). MDR-TB patients with diabetes were 7.65 times more likely to develop severe adverse effects compared to those patients without diabetes mellitus (AOR =7.65, 95% CI = 1.15-50.62).

## DISCUSSION

A high incidence rate of adverse effects was noted in 219 (92%) of the 238 patients and treatment had to be suspended due to adverse effects in 46 (19.3%) cases. This finding is consistent with that of a study in northern Lima, which showed that one or more drugs were suspended only in 20% of patients (14). However, another study in the USA reported that 30% of patients had adverse effects requiring discontinuation of one or more anti-tuberculosis medications. Lower tolerance to adverse effects and the possibility of switching from drug to drug in USA patients might be the reason for a higher rate of adverse effect (16).

In this study, 8.8 % of patients were new cases and 91.2% were registered after having a history of 1$^{st}$ line anti TB treatment. This showed that acquired resistance was higher than the primary resistance in our cohort. This finding was supported by an Egyptian study which found out that the acquired MDR-TB cases (95.3%) exceeded the primary MDR-TB cases (4.7%) (17). Which is an alarming finding and implies spread of infectious resistant strains in the community.

In our study, the HIV and MDR_TB co-infection rate (13.4%) was lower than the rate reported by a study in Western Cape Town, which showed a co-infection rate of 72.6 % (4). This difference may reflect the higher HIV disease burden in Cape Town. However, another study in Peru showed a lower MDR-TB/HIV co-infection rate (1.7%). A lower rate in this study might be due to the small sample size, i.e., 60 patients (9).

Patients in our study had received a mean of 5.3 drugs, which was higher in a study conducted in Lima, Peru where a median of 3 (1–8) anti-tuberculosis regimens were administered (8). This may be due to the fact that most of the patients (49.2%) in our study were registered after failure of retreatment, which needs multiple drugs. A cohort of MDR-TB patients in Lima Peru in 1999 received a median of 8.0 (5–12) anti-tuberculosis drugs with at least one parenteral agent (9). This discrepancy may have resulted from the difference in the study period, and some of the drugs are excluded nowadays.

In this study, gastrointestinal effect has been found to be a frequently occurring side effect (73.1%). This is consistent with findings from other studies (7, 9, 14, 18, and 19).

Hypokalemia (45.4%) was the second most frequently observed adverse effect, and it is attributed to Capreomycin. This finding was more or less consistent with that of a study conducted in Lima, Peru (20); which was observed in 31.3% of cases. Hypokalemia was reported in 31.9% of patients in a previous study conducted in Addis Ababa (14). Similarly, a lower level of hypokalemia (23%) was seen in a study conducted in India (21). The limited use of ancillary medications, like potassium chloride (Kcl) may be attributed to the higher rate of hypokalemia in our study.

A higher frequency of arthralgia (46.6%) was reported in a previous study from Addis (14), than 29.4% of patients observed in our study. However, a study conducted in Durban, South Africa documented arthralgia in 15.9% of cases (15). A lower frequency of arthralgia (4.15%) was showed in a study conducted in India (18). Frequent use of Pyrazinamide (Z) could be the reason for higher frequency of arthralgia in our study.

Some adverse effects were less common in this study than in other studies (5, 7, 9 and 14). In our study, psychiatric problems were seen in 7.2% of cases, hypothyroidism in 5.9%, renal toxicity in 5%, hepatotoxicity in 0.8% cases and Ototoxicity in 0% cases. These findings contrast with other reports (5, 9, and 14). Ototoxicity (41.8%) and psychiatric disorders (21.3%) were frequently seen in a cohort study in Istanbul (5), Similarly, psychiatric episodes (13%), hepatitis (9%), and renal failure (4%) were relatively frequent as shown by a study conducted in Latvia (7). In the current study setup, patients suspected for such types of severe problems were usually referred to a specialty doctor.

Due to this, adverse effects could not be documented properly. Moreover, limitation of diagnostic methods for these problems might be the contributing factor for a lower episode of these adverse effects in our study.

In this study, co-morbid conditions of HIV/AIDS and diabetes mellitus, older age group, and being homeless were the significant predictors of severe adverse effect. HIV/MDR-TB co-infection was found to be a significant predictor of severe adverse effects in our study. This finding was supported by a qualitative study conducted in Mumbai, India, which showed that side effects of drugs among HIV/MDR-TB co-infected patients were reported to be severe and debilitating, and patients expressed the burden of care and stigma on the social and financial viability of the household (22). This is not in accordance with a study in South Africa which reported no significant difference in adverse effect frequency between subjects who were or were not treated with concomitant ART and concluded that concurrent treatment for MDR-TB/HIV can be safely administered in a home-based care setting (23). A better clinical presentation and the World Health Organization's (WHO) staging of disease among patients in South Africa might be the reason for this discrepancy. Severe adverse effects were significantly associated with diabetes/ MDR-TB co-infection in our study. Likewise, a study in Egypt found that DM/MDR-TB co-infection was an important predictor of severe adverse effect among MDR-TB treated patients (17). In such a case, Ethambutol dosing frequency should be decreased when patients with diabetes have reduced kidney function (24). In the current study, severe adverse effect was significantly associated with older age group. A similar finding was showed in a study conducted in Addis Ababa and Lima, Peru (14, 25).

The main limitation of this study is that the diagnosis of adverse effects could not be performed prospectively. Rather it was based on what was registered in the medical record. This may result in an underestimate of the prevalence of some of the adverse effects in our study. Despite this limitation, the study tried to address an important public health problem - severe adverse effects of MDR-TB therapy, which has not been addressed in local studies so far.

## CONCLUSION

In conclusion, a high incidence rate of severe adverse reactions to second - line anti-TB drugs were noted, and resulted in the suspension of one or more drugs. Adverse effects observed most frequently include: gastrointestinal effect, hypokalemia, arthralgia, sleep disturbance and psychosis.

Comorbid conditions of HIV/AIDS and diabetes mellitus, older age group and being homeless were the important predictors of severe adverse effects. However, most adverse effects were either tolerated by patients or were relieved with ancillary medications. Although regimens were adjusted and suspended, total discontinuation of second line anti TB drug due to the occurrence of an adverse effect was never indicated. All diagnostic tests and ancillary medications need to be always available for early detection, treatment and follow up of adverse events. Patients need to be aware of the seriousness of their condition and the absence of options for cure if they choose to discontinue therapy. Special attention should be given to the elderly, homeless, HIV/MDR-TB and diabetes/MDR-TB co-infected patients.

The different types of adverse events associated with second - line anti-TB drugs are already known. However, it is not clear whether or not these adverse events led clinicians to discontinue therapy. In addition, who is more at risk of second - line anti-TB drug adverse effect was not clearly shown in previous studies. What is new to this study is **t**hat it showed the incidence of adverse events which led the clinician to discontinue therapy in the local context. We investigated total discontinuation of second line anti TB drugs due to the occurrence of an adverse effect; this was not indicated except for temporary discontinuation (suspension) of drugs.
This study showed second line anti-TB therapy adverse effects were associated with HIV/AIDS infection, having diabetes mellitus, being elderly and being homeless.

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***Competing interests***
Authors declared they have no conflict of interest.

***Authors' Contribution***

Yimer wrote the proposal, led the data collection and supervision activity, analyzed the data, and drafted the manuscript. Bezawit, Mengistu, and Zelalem approved the proposal with some revisions, participated in supervision and data processing. All the authors revised subsequent drafts of the paper, read and approved the final manuscript.

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