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# Treatment-Associated Adverse Effects in Patients with Multidrug-Resistant Tuberculosis: A Study from Khyber Pakhtunkhwa

Ubaid Ullah<sup>1</sup>, Afsar Khan Afridi<sup>2</sup>, Touqeer Anjum<sup>3</sup>

<sup>1</sup>Programmatic Management of Drug-Resistant TB Unit, Mardan Medical Complex, Mardan - Pakistan  
<sup>2</sup>Health Department, Khyber Pakhtunkhwa - Pakistan  
<sup>3</sup>Programmatic Management of Drug-Resistant TB Unit, Lady Reading Hospital Peshawar - Pakistan

## Corresponding Author:

**Afsar Khan Afridi**  
 Health Department,  
 Khyber Pakhtunkhwa - Pakistan  
 E-mail: [afsarafriidk@yahoo.com](mailto:afsarafriidk@yahoo.com)

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## ABSTRACT

**Background:** Pakistan ranks fourth among the 22 high-burden countries for multidrug-resistant tuberculosis (MDR-TB). The rising incidence of MDR-TB highlights the need for effective treatment programs, as the clinical management of MDR-TB involves prolonged multidrug regimens that frequently result in adverse events (Aes).

**Objective:** This study aims to determine the frequency of treatment-related adverse events among patients enrolled in MDR-TB treatment.

**Methodology:** We conducted a retrospective case series study involving patients enrolled for MDR-TB treatment from January 2020 to April 2022 at the Programmatic Management of Drug-Resistant TB (PMDT) unit of Lady Reading Hospital (LRH) in Peshawar, Pakistan. Patient data were recorded in an Electronic Nominal Record System (ENRS). Statistical analysis was performed using SPSS software, with subjective data assessed through the Chi-Square test and quantitative data analyzed using Student's t-test. Both univariate and multivariate regression models were employed to explore the relationship between medication-related adverse reactions and treatment outcomes, setting a significance threshold at  $p < 0.05$ .

**Results:** The study included 411 MDR-TB patients undergoing treatment. Of these, 360 patients were analyzed, comprising 212 (51.6%) males and 148 (36%) females, predominantly aged between 15-44 and 45-64 years. The most frequently reported side effects were psychiatric symptoms (67%), gastrointestinal issues (58.5%), ototoxicity (49.5%), and arthralgia/arthritis (48.7%). Psychiatric symptoms affected 241 (67%) patients, with 91 (25.3%) experiencing major adverse events. In contrast, 150 (41.6%) cases of adverse events were classified as non-serious and managed through additional medications or dosage adjustments.

**Conclusion:** Adverse events are common among MDR-TB patients treated at PMDT-LRH Peshawar. Younger patients and those with cavitary lung disease should be monitored closely for the development of adverse events to enhance patient safety and treatment efficacy.

**Keywords:** Multidrug Resistant TB; Adverse Events; Peshawar; Pakistan

## Introduction

**T**uberculosis, second leading cause of death by a biological agent after HIV is caused by *Mycobacterium tuberculosis*. MDR-TB refers to resistance to two most powerful anti-TB drugs of Rifampicin and Isoniazid and is a man-made problem that is increasing in low economic countries. Pakistan stands 5<sup>th</sup> among 22 high endemic countries with new 518,000 TB cases and estimated 15,000 MDR-TB cases reported in 2021 and the 1<sup>st</sup> country with huge toll of MDR-TB in Eastern Mediterranean region.<sup>1</sup> As living in low income state, we are still at risk of having an increase in these numbers of MDR-TB. The young population is at great risk of developing MDR-TB. Reasons behind emergence of drug resistant strain is the result of inadequate drug regimen prescribed by physicians, close contact with an index case, maladministration and irregular intake of prescribed medications by patient itself along with medication non-adherence. Sometimes, medication used for treatment and cure can force major unfavorable effects and the analogous coincide with the treatment and medications of MDR-TB. Anti-TB medications include FLDs such as Isoniazid, Rifampicin, Ethambutol, Pyrazinamide and Streptomycin while Kanamycin, Capreomycin, Amikacin, Levofloxacin, Moxifloxacin, Bedaquilin, Linezolid, Clofazimine, Cycloserine, Delamanid, Amikacin, Ethionamide and p-aminosalicylic acid are considered SLDs/ Fluoroquinolones.<sup>2</sup> The treatment against MDR-TB is expensive, long and have many toxic and adverse effects on the health of the patients. After the initiation of Programmatic Management of Drug-Resistant Tuberculosis (PMDT) in 2010, two year long term treatment regimen (LTR) was introduced for RR/MDR-TB but due to some reasons, this LTR was replaced by short treatment regimen (STR) in 2018. The duration of this treatment was believed to be between 9-11 months with least or reduced chances of fluoroquinolones resistance and increased possibility of efficiency that has been found to be higher than 80%.<sup>3</sup> The treatment is designed according to individual's BMI along with type of resistance and is delivered through a community based program. Since due to lengthy and toxic chemotherapy, these patients experience various psychological and physiological effects on their health that include depression, anxiety, suicidal ideations and psychosis.<sup>4</sup> Along with these dilemmas, they also experience stigma, fear of isolation and humiliation by society. During this time period, majority of the patients complaint about hearing loss and optic neuritis. While other studies reported other physiological effects as gastro-intestinal issues along with arthralgia, hepatitis, arthritis, peripheral neuropathy, hypothyroidism, epilepsy, dermatological issues and neurotoxicity and require the discontinuation of the therapy. GIT problems were observed mainly due to side effects of Ethambutol and *para* aminosalicylic acid

whereas depression and other psychological issues such as nausea and vomiting were observed due to Cycloserine, Isoniazid, Rifampicin, Fluoroquinolones and Ethambutol.<sup>4</sup> Other literature also reported sleeping disorders, eating disorders and visual impairment as well as abdominal pain.<sup>2,4</sup> These Anti-TB medications that pose adverse effects on the infected individuals, may be a factor leading towards treatment non-adherence. Thus, this medication non-adherence proceed towards an increase burden of MDR-TB in the country.

This study was conducted to find out adverse side effects faced by MDR-TB patient treated for MDR-TB treatment at PMDT unit, Lady Reading Hospital Peshawar, Pakistan.

## Objective

To know the frequency of occurrence of treatment related adverse events among enrolled MDR-TB patients.

## Methodology

In Pakistan, MDR-TB is treated under the Programmatic Management of Drug-Resistant Tuberculosis which is supervised by National Tuberculosis Programme. This cohort study was conducted at PMDT LRH Peshawar, Pakistan, to evaluate the adverse side effects these patients experienced due to SLDs during their anti-TB treatment.

The medications were given to the patients according to their monthly Drug susceptibility reports. The treatment routine comprising of Amikacin (15 mg/kg, maximum 1000 mg everyday), Levofloxacin (750 mg every day), Cycloserine (10-20 mg/kg, maximum 1000 mg daily), Ethionamide (10-20 mg/kg, 1000 mg every day) and Pyrazinamide (20-30 mg/kg, maximum 2000 mg every day). In the wake of DST results, routine is individualized for every patient. Aminoglycosides were directed for the base time of 8 months, and different medications for least 20 months.

At time of their enrollment, each patient was screened for the presence of any other illness and this was practiced each month on their monthly follow up by physicians and psychologists using a standardized module which include all the complaints/ adverse effects ranging from mild headache to other severe physiological change due to these SLDs.

All the information of patient was constituted into an Electronic Nominal Record (ENRS). The results were analyzed utilizing SPSS (SPSS adaptation 16, SPSS Inc). Subjective information were analyzed utilizing Chi-Square test. Quantitative information were analyzed utilizing Understudy's t-test. Univariate and multivariate regression models were utilized to find the association between the adverse reactions of the medications with poor treatment result. The significance level was set at  $p < 0.05$ .

## Results

This study was performed among 411 MDR-TB patients, taking the TB medications. Among these enrolled patients 360 individuals showed complications after taking the drugs. Out of these 360 patients 212 (51.6%) were male and 148 (36%) were female, mostly from the age group of 15-44 and 45-64. Among these patients 55.6% patients belonged to the rural areas. Also 47.4% patients showing adverse effects of drugs had received TB treatment for less than a year and 40.2% had TB drugs for more than 1 year prior to this visit. Out of these patients only 20% received second-line drugs. Although despite having the TB disease, 41.1% patients did not have any cavitation in the lungs upon x-ray while 23.1% had bilateral cavitation and lastly 23.3% patients showed unilateral cavitation. Failure of previous treatment was observed in both category I and category II failure groups, constituting about 37.5% and 35% patients (Table 1).

The most common side effects seen in patients were Psychiatric symptoms (67 %), gastrointestinal problems (58.5%), ototoxicity (49.5%) and arthralgia/arthritis (48.7%). Psychiatric symptoms were observed in 241(67 %) patients. This includes wide range of symptoms which include depression, anxiety, psychosis and suicide. The patients with major side effects included 91 (25.3%) cases while 150 (41.6%) cases containing these symptoms were not serious and were controlled by additional medications or by changing the drug dose.

Gastrointestinal side effects were seen in 211 (58.5%) patients and out of these cases 9 (2.5%) patients had major reaction towards the drugs and thus their medication was either replaced or the drugs causing the side effects were eliminated completely. Remaining 202 (56.1%) patients had minor gastrointestinal problems. The symptoms also included vomiting, diarrhea, nausea and anorexia.

Ototoxicity includes tinnitus, hearing problems and vertigo and these symptoms were observed in 178 (49.5%) patients. 8 (2.2%) cases of side effects were not serious but majority 170 (47.2%) cases had serious side effects and ended in withdrawal of drugs that were causing it.

Arthralgia was observed in 175 (48.5%) patients and 122 (33.9%) patients had minor side effects of the medication while 53 (14.7%) expressed adverse reactions to the medication.

Hepatitis was caused by the medication in 15 (4.2%) patients .4 (1.1%) had minor side effects but 11 (3.1%) had major adverse reactions.

Problems associated with Central Nervous system included 26 (7.2%) patients and 15 (4.2%) cases did not show any serious reaction but 11 (3.1%) cases showed severe reactions to the medication. Thus, the medication was either replaced or eliminated and sometimes dosage was altered for successful treatment outcomes.

Dermatological effects including skin rash was reported in

25 (6.9%) patients and in 21 (5.8%) cases it became a serious health concern while in 4 (1.1%) cases minor complications were observed.

Peripheral neuropathy was seen in 11 (3%) patients and out of these 8 (2.2%) had major side effects while 3 (0.8%) had minor effects on patients. It includes numbness and tingling of hands and feet as well as burning sensations in the affected areas.

Renal toxicity was seen in only 4 (1.1%) patients but all these patients had experienced severe side effects on the kidney functions hence the drug causing kidney problems was removed.

Hypothyroidism was seen in 2 (0.6%) patients and they had minor side effects of the drugs.

## Discussion

South Asia contributes about 40% of tuberculosis disease burden globally. Literature suggest that about 70% of cases remains untreated. Among 360 of the 411 patients, side effects had been observed, and treatment had to be modified due to side effects in 205(57%), which is higher than previously recorded in the literature.<sup>4,5,6,7</sup>

Our study patients belong to the age group of 15-44 and 45-65. Contradicting to our findings a study done in china by Zhu et al., from 2010 to 2015 suggested an increase incidence of TB disease among children both under 5 and 5-14 years while in another study done on 136394 confirmed TB cases from 2007 to 2012 by Li et al., suggested an increasing TB incidence in patients aged 45-64 which is quite similar to our findings.<sup>8</sup>

The prevalence of recurrent TB in urban areas was higher than rural areas (15.3% and 11.3%) in a study done in Southern Province of Zambia by Mutembo et al., which is contrary to our findings. In our observations 55.6 % patients belong to rural areas and literacy rate in rural areas is much lower than urban population. This lack of education leads to limited knowledge about the TB disease and its prevention. Also completion of treatment is successful in urban areas as compared to the rural areas. Similarities were found in a study done in Oryol Region by which shows higher incidence of TB disease in rural areas.

The frequent and early onset of ototoxicity in our patients may be attributed to prolonged exposure to aminoglycosides and capreomycin during or prior to their MDR-TB treatment. This aligns with the findings of Moore et al., who identified a correlation between the cumulative duration of aminoglycoside use and the incidence of ototoxicity.<sup>10</sup> In contrast, a study by Sharma et al. reported hearing issues and tinnitus in 14.1% of patients, a figure that significantly differs from our observations.<sup>11</sup> In our study, nephrotoxicity associated with aminoglycosides was found in only 1.1% of patients, a rate that is lower than the prevalence of ototoxicity (49.5%) and comparable to results reported in other studies, such as that by Javaid et al. in 2017.<sup>12</sup>

Table 1. Baseline characteristics of study cases

Characteristics	No Adverse Effects N=51	Adverse Effects N=360
<b>Gender</b>		
Male	27 (6.6%)	212 (51.6%)
Female	24 (5.8%)	148 (36.0%)
<b>Age (years)</b>		
≤14	2 (0.5%)	14 (3.4%)
15-44	26 (6.3%)	170 (41.4%)
45-64	22 (5.3%)	132 (32.1%)
≥65	1 (0.2%)	44 (10.7%)
<b>Weight (kg)</b>		
<40	12 (2.9%)	97 (23.6%)
40-60	28 (6.8%)	183 (44.5%)
>60	11 (2.7%)	80 (19.5%)
<b>Residence</b>		
Urban	19 (4.6%)	132 (32.1%)
Rural	32 (7.8%)	228 (55.6%)
<b>Marital Status</b>		
Married	39 (9.5%)	220 (53.5%)
Unmarried	12 (2.9%)	138 (33.6%)
Widow	0	2 (0.5%)
<b>Previous TB Treatment Episodes</b>		
Less than or equal to 1 year	31 (7.5%)	195 (47.4%)
Greater than 1 year	20 (4.9%)	165 (40.2%)
<b>Previous use of second-line Drugs</b>		
Yes	14 (3.4%)	83 (20.0%)
No	37 (9.0%)	277 (67.4%)

<b>Registration group</b>		
New	3 (0.7%)	26 (6.3%)
Relapse	7 (1.7%)	36 (8.8%)
Category I Failure	19 (4.6%)	154 (37.5%)
Category II Failure	22 (5.4%)	144 (35.0%)
<b>Lung cavitation at baseline chest X-ray</b>		
No cavitation	23 (5.6%)	169 (41.1%)
Unilateral cavitation	10 (2.4%)	96 (23.3%)
Bilateral cavitation	18 (4.4%)	95 (23.1%)

Psychiatric disorders were frequently observed in this study. Prevalence of Depression was very low (16.2%) in a study conducted by Sharma et al., which is opposite to our findings.<sup>11</sup> However, 31.5% prevalence rate was seen in pulmonary clinical visits and 45.5% psychiatric disorders were observed in contact TB patients in a study done in Nigeria by Ige et al. This factor may attribute to a loss of confidence in the health services. In order to continue long term treatment regimen patient trust is another important factor to gain confidence. PMDT physicians and managers need to strive hard to build trust and confidence in patients in order to achieve compliance and successful treatment. The two side effects psychosis and depression needed antidepressant or anti-psychotic therapy as and when needed. Therefore, PMDT initiated antipsychotic and antidepressant therapy on priority basis. Similarly, Patients exhibiting suicidal tendencies were prioritize for hospitalization. Furthermore, if the medication failed to control psychiatric side effects, Cycloserine was either withdrew or suspended up till symptoms were resolved. Fluoroquinolones are very effective and are central to MDR-TB treatment regimens. Our preference was therefore to retain fluoroquinolones in the regimens while controlling their side effects. Psychiatric problem in the current study was the leading cause of drug withdrawal.

Dermatological issues like darkening of skin and rashes were seen in 6.9% sample. However, higher number of patients (34.6%) had this complain in a study done by Sharma et al., in Ahmedabad city, India.<sup>11</sup>

Javaid et al. (2022) reported that therapies based on preotamanid and delamanid are most frequently associated with gastrointestinal side effects. In our study, gastrointestinal disorders were identified as the second most common adverse effects, affecting 58.6% of patients, following psychiatric disorders.<sup>1</sup> This finding is consistent with research conducted in Ahmedabad, where 43.2% of patients experienced gastrointestinal

tract issues (Sharma et al., 2022).<sup>11</sup> The presence of these side effects can significantly impact patients' quality of life and adherence to treatment, highlighting the need for proactive management strategies. It is crucial for healthcare providers to educate patients about potential gastrointestinal disturbances and offer dietary modifications or supportive care to mitigate these effects.

Hepatotoxicity was noted in 4.2% of our sample, necessitating the suspension of all medications until liver function tests return to baseline levels. Once the patient's liver function stabilizes, it is recommended to reintroduce the medications gradually, starting with lower doses and increasing them incrementally. This approach helps in minimizing the risk of exacerbating liver damage. It is important to add drugs associated with hepatotoxicity last to avoid further complications. Monitoring liver function is essential during the treatment regimen, as early detection of hepatotoxicity can facilitate timely interventions and prevent severe outcomes.

Arthralgia was reported in 48.5% of the patients in our study, indicating a significant burden of joint pain among those undergoing MDR-TB treatment. In contrast, a study by Sharma et al. showed only 2.7% of patients presenting with arthralgia. The discrepancy suggests that our patient population may be particularly susceptible to musculoskeletal side effects, which can lead to non-compliance with treatment due to discomfort. Addressing this issue through physical therapy, analgesics, or alternative therapies could enhance the overall patient experience.

Our findings underscore the high rate of side effects associated with MDR-TB treatment; however, these adverse events should not deter clinicians from continuing the treatment regimen in such cases. Effective management of side effects is essential to maintaining patient adherence and improving treatment outcomes. Therefore, it is imperative to implement timely and optimal management strategies for any adverse effects encountered. Regular clinical monitoring, comprehensive

Table 2. Frequency of side effects experience during study time

Side Effects	Patients experiencing the side effects n (%)	Minor effects: Do not need to withdraw the drug n (%)	Major effects: Needed to withdraw the drug n (%)
Psychiatric symptoms	241 (67%)	8 (2.2%)	170 (47.2%)
Gastrointestinal problems	211 (58.5%)	150 (41.6%)	91 (25.3%)
Ototoxicity	178 (49.5%)	169 (47%)	9 (2.5%)
Arthralgia/arthritis	175 (48.5%)	122 (33.9%)	53 (14.7%)
Hepatitis	15 (4.2%)	4 (1.1%)	11 (3.1%)
Central Nervous system	26 (7.2%)	15 (4.2%)	11 (3.1%)
Dermatological effects	25 (6.9%)	4(1.1%)	21 (5.8%)
Peripheral neuropathy		3 (0.8%)	8 (2.2%)
Renal toxicity	4 (1.1%)	-	4 (1.1%)
Hypothyroidism	2 (0.6%)	2 (0.6%)	-

laboratory assessments, and a multidisciplinary team approach are critical components in the follow-up care of MDR-TB patients. This holistic approach ensures that all aspects of patient health are addressed, ultimately contributing to more successful treatment outcomes and improved patient satisfaction.<sup>7,12,13</sup>

## Conclusion

While adverse reactions are prevalent among MDR-TB patients, they do not constitute a significant barrier to the implementation of PMDT projects. This study emphasizes the importance of pre-treatment counseling and continuous support throughout the treatment process to enhance patient adherence and minimize dropout rates. By reflecting real-world MDR-TB treatment practices, this research provides valuable insights for clinicians, suggesting that targeted management strategies for younger and more severely affected patients are crucial for optimizing treatment outcomes.

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