Section: Respiratory Medicine

Original Research Article

ADVERSE DRUG REACTION PROFILE AND TREATMENT OUTCOMES IN DRUG-RESISTANT TUBERCULOSIS UNDER THE NATIONAL TUBERCULOSIS ELIMINATION PROGRAMME: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background:Objectives: Drug-resistant tuberculosis (DR-TB) treatment under the National Tuberculosis Elimination Programme (NTEP) involves complex, long-duration multi-drug regimens associated with frequent adverse drug reactions (ADRs). This study aimed to determine the incidence, clinical spectrum, severity, onset timing, management strategies, and final treatment outcomes of ADRs among patients receiving DR-TB therapy at a tertiary care teaching hospital in Western India.

Materials and Methods: A prospective observational study was conducted in the Department of Respiratory Medicine at a tertiary care center in Ahmedabad from December 2023 to January 2026. One hundred consecutive adult patients with microbiologically or genotypically confirmed DR-TB initiated on NTEP-recommended regimens (longer oral MDR/RR-TB, BPaLM, shorter oral MDR/RR-TB, and isoniazid mono/poly-DR-TB) were enrolled. Patients underwent standardized pre-treatment evaluations and protocolized clinical, laboratory, radiological, and electrocardiographic monitoring during follow-up visits. ADR severity (mild, moderate, severe), onset time, management interventions (drug hold/rechallenge, dose modification, permanent withdrawal), and treatment outcomes (cure, completion, failure, death, loss to follow-up) were systematically documented.

Results: Among 100 patients (63 men, 37 women; mean age 36.8 yr, range 15–72 yr), 84% were underweight (BMI <18.5 kg/m²) and 78% belonged to lower socioeconomic strata. Regimens comprised longer oral MDR/RR-TB (69%), BPaLM (20%), shorter oral MDR/RR-TB (8%), and isoniazid mono/poly-DR-TB (3%). All 100 patients experienced at least one ADR. Severity was mild in 65%, moderate in 20%, and severe in 15%. Onset occurred within <1 month in 31%, 1–2 months in 10%, and >2 months in 59%. Peripheral neuropathy (43%, linezolid/cycloserine) and skin discoloration (42%, clofazimine) were the most frequent ADRs, followed by gastritis (18%), arthralgia (7%), hepatotoxicity (6%), nephrotoxicity (4%), alopecia (3%), optic neuropathy (2%), allergic skin reactions (2%), psychiatric symptoms (2%), diarrhea (2%), QTc prolongation/VPCs (2%), myelosuppression (1%), and seizures (1%). Management involved drug hold and rechallenge in 85%, drug modification in 11%, and permanent withdrawal in 4%. Overall treatment success was 91% (80% cured, 11% completed), with 6% lost to follow-up, 2% mortality, and 1% treatment failure.

Conclusions: Adverse drug reactions were universal in DR-TB patients receiving all-oral NTEP regimens, but the vast majority were mild-to-moderate and successfully managed using structured protocolized interventions without

compromising treatment success. Although late-onset cumulative toxicity predominated, severe early-onset reactions highlight a critical window for intensified active drug safety monitoring (aDSM). Programmatic integration of active ADR surveillance and timely conservative management is essential to enhance patient safety and support national TB elimination goals.
Keywords: Adverse drug reactions; Bedaquiline; BPaLM regimen; Drug-resistant tuberculosis; Linezolid; National Tuberculosis Elimination Programme; Pharmacovigilance.

INTRODUCTION

Tuberculosis (TB) remains a major global public health threat and a leading cause of mortality from a single infectious agent worldwide. According to the World Health Organization (WHO) Global TB Report 2025, an estimated 10.6–10.8 million people fell ill with TB globally in 2024, resulting in 1.23 million deaths.[1] India bears the highest burden of TB globally, accounting for over 26% of all global cases, with an estimated 2.85 million incident TB cases and 320,000 deaths reported in 2024.[1,2]

The emergence and continuous spread of drug-resistant tuberculosis (DR-TB)—including multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB), pre-extensively drug-resistant TB (pre-XDR-TB), and extensively drug-resistant TB (XDR-TB)—presents a formidable challenge to global tuberculosis control.[3,4,6] In India, an estimated 6–7% of notified TB cases exhibit MDR/RR-TB, translating to over 6,000 cases annually in Gujarat state alone.[2,4] DR-TB treatment regimens are inherently complex, characterized by prolonged treatment durations, substantial pill burdens, high financial expenditures, and significant drug toxicity.

Under the National Tuberculosis Elimination Programme (NTEP), management of DR-TB has undergone a major paradigm shift away from injectable-containing regimens toward standardized, all-oral, bedaquiline-based treatment regimens.[3,4,6] Current NTEP treatment guidelines encompass longer all-oral MDR/RR-TB regimens (18–20 months), shorter all-oral MDR/RR-TB regimens (9–11 months), isoniazid mono/poly-drug resistant TB (Hr-TB) regimens (6–9 months), and novel shorter all-oral regimens such as BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin, 26–39 weeks).[4,6,9] While these all-oral regimens have markedly improved treatment completion and microbiological cure rates, the inclusion of potent second-line agents—notably linezolid, bedaquiline, pretomanid, fluoroquinolones, clofazimine, and cycloserine—is accompanied by a distinct and frequently severe spectrum of adverse drug reactions (ADRs).[10,11,23]

Adverse drug reactions constitute a primary determinant of treatment non-adherence, temporary drug interruption, permanent regimen modification, secondary drug resistance amplification, treatment failure, and patient morbidity or mortality.[10,11,23] Unmanaged ADRs also place an immense psychosocial and financial burden on patients, who frequently belong to socioeconomically vulnerable populations. Despite the widespread rollout of all-oral regimens under NTEP, real-world data regarding the comprehensive spectrum, severity, onset timing, management outcomes, and clinical risk factors of ADRs in Western Indian populations remain limited.[17,18,20,22]

We therefore undertook a prospective observational study of patients with drug-resistant tuberculosis receiving standardized NTEP regimens at a tertiary-care teaching hospital in Western India. The primary objective was to evaluate the incidence, clinical spectrum, severity, and temporal onset of ADRs. Secondary objectives were to analyze the effectiveness of protocolized management strategies (drug hold/rechallenge, dose modification, permanent drug withdrawal) and evaluate their impact on final treatment outcomes.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was conducted in the Department of Respiratory Medicine and the specialized DR-TB Nodal Centre at Narendra Modi Medical College and Sheth L.G. General Hospital, Maninagar, Ahmedabad, Gujarat, India, between December 2023 and January 2026. The study protocol was developed in accordance with the technical and operational guidelines of the National Tuberculosis Elimination Programme (NTEP) and reported following the STROBE guidelines for prospective observational cohort studies.

Participants

Adult patients (aged 18 years and above) with microbiologically or genotypically confirmed drug-resistant tuberculosis (MDR/RR-TB, pre-XDR-TB, XDR-TB, or Hr-TB) who were initiated on standardized NTEP treatment regimens at the DR-TB Centre were eligible for inclusion. Confirmation of diagnosis and resistance profiling were established using WHO-endorsed rapid molecular diagnostics (Cartridge-Based Nucleic Acid Amplification Test [CBNAAT/Xpert MTB/RIF], First-Line Line Probe Assay [FL-LPA], Second-Line Line Probe Assay [SL-LPA]) and automated liquid culture and drug susceptibility testing (Mycobacteria Growth Indicator Tube [MGIT 960]). Patients were included if they provided written informed consent and were willing to adhere to routine follow-up schedules. Patients with drug-susceptible TB, those transferred

out to non-affiliated centers prior to ADR baseline assessment, or those unwilling to participate were excluded.

Pre-treatment evaluation and treatment regimens

Prior to initiating DR-TB therapy, all enrolled patients underwent a thorough pre-treatment evaluation protocol as mandated by NTEP guidelines. This included detailed medical history, physical examination, baseline weight and body mass index (BMI) calculation, socioeconomic status categorization using the Modified Kuppuswamy scale, complete blood count (CBC), liver function tests (LFT: serum bilirubin, SGPT/ALT, SGOT/AST, total protein, albumin), renal function tests (RFT: blood urea, serum creatinine), serum electrolytes (sodium, potassium, calcium, magnesium), blood glucose, thyroid-stimulating hormone (TSH), urine pregnancy test (UPT) for women of childbearing age, baseline chest radiography (CXR-PA view), and a 12-lead electrocardiogram (ECG) with corrected QT (QTc) interval assessment using Fridericia's formula (QTcF).

Treatment regimens were prescribed strictly according to NTEP eligibility criteria:

1. Longer Oral MDR/RR-TB Regimen (18–20 months): Comprising bedaquiline (Bdq, 6 months or extended), levofloxacin (Lfx), linezolid (Lzd), clofazimine (Cfz), and cycloserine (Cs), prescribed for patients with fluoroquinolone resistance, extensive/cavitary parenchymal disease, or previous second-line drug exposure.
2. BPaLM Regimen (26–39 weeks): Comprising bedaquiline, pretomanid (Pa), linezolid (600 mg daily for 9–13 weeks, optionally reduced to 300 mg), and moxifloxacin (Mfx), indicated for eligible non-pregnant adults with MDR/RR-TB without prior exposure to second-line drugs.
3. Shorter Oral MDR/RR-TB Regimen (9–11 months): Comprising an intensive phase with bedaquiline, levofloxacin, clofazimine, pyrazinamide (Z), ethambutol (E), high-dose isoniazid (Hh), and linezolid, followed by a continuation phase.
4. Isoniazid Mono/Poly DR-TB (Hr-TB) Regimen (6–9 months): Comprising levofloxacin, rifampicin (R), ethambutol, and pyrazinamide (Lfx-R-E-Z).

ADR monitoring, severity grading, and temporal classification

A structured active drug safety monitoring (aDSM) protocol was implemented throughout the treatment period. Patients were evaluated clinically on a biweekly basis during the initial two months and monthly thereafter, or immediately upon presenting with any un-forward symptoms. Follow-up laboratory evaluations included biweekly CBC and monthly LFT, RFT, serum electrolytes, and ECG for the first 6 months, with TSH monitored every 6 months. Audiometry, visual field and color vision testing, psychiatric assessments, and uric acid measurements were performed when clinically indicated.

An Adverse Drug Reaction (ADR) was defined per WHO criteria as any response to a drug that is noxious and unintended, occurring at doses normally used in humans. ADR severity was graded using standardized NTEP/CTCAE criteria:

- **Mild (Grade 1):** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with normal daily activities.
- **Moderate (Grade 2):** Discomfort sufficient to cause interference with normal activity, requiring targeted medical therapy or dose adjustment.
- **Severe (Grade 3–4):** Extreme distress causing significant functional impairment, incapacitation, or life-threatening risk, requiring immediate drug interruption, hospitalization, or regimen substitution.
- The temporal onset of ADRs from treatment initiation was categorized into three distinct windows: early-onset (<1 month), intermediate-onset (1–2 months), and late-onset (>2 months / >4 months). Causality assessment was performed using the WHO-UMC scale, and suspected reactions were reported via official Pharmacovigilance Programme of India (PvPI) forms.

Management interventions and final treatment outcomes

ADRs were managed according to standardized NTEP operational algorithms:

1. Drug Hold and Rechallenge: Temporary withholding of offending drug(s) until symptom resolution or laboratory normalization, followed by sequential rechallenge or symptomatic support (e.g., antacids, NSAIDs, antihistamines, pyridoxine, antiemetics).
2. Drug Modification: Dose reduction of offending agents (e.g., reducing linezolid from 600 mg to 300 mg daily for Grade 2 neuropathy or myelosuppression, or cycloserine reduction for nephrotoxicity).
3. Permanent Withdrawal: Permanent discontinuation of the causative drug with replacement by an alternative effective second-line agent (e.g., stopping linezolid and substituting ethambutol for severe neuropathy; stopping cycloserine and substituting pyrazinamide for seizures; stopping bedaquiline and substituting delamanid for severe QTc prolongation).

Final treatment outcomes were defined according to standard NTEP and WHO definitions: Cured (bacteriologically confirmed negative at treatment end without failure), Treatment Completed (completed treatment without bacteriological proof of cure but no evidence of failure), Lost to Follow-up (treatment interrupted for 2 consecutive months or more), Died (death due to any cause during treatment), and Treatment Failed (regimen terminated or permanently shifted to a new regimen option due to clinical/microbiological failure or severe unmanageable drug toxicity). Overall

treatment success was defined as the sum of cured and treatment completed cases.

Statistical analysis

Data were compiled into Microsoft Excel and analyzed using standard statistical methods. Quantitative variables were expressed as mean, median, standard deviation, and range. Categorical variables were summarized as absolute frequencies and percentages. The association between baseline body mass index (categorized as underweight [<18.5 kg/m²] vs. normal/overweight [≥18.5 kg/m²]) and ADR severity (mild vs. moderate/severe) was evaluated using Fisher's exact test, with odds ratios (OR), 95% confidence intervals (95% CI), and p-values computed. A p-value of <0.05 was considered statistically significant.

Ethics and consent

The study protocol was reviewed and approved by the Institutional Review Board (IRB) and Ethics Committee of Narendra Modi Medical College, Ahmedabad (Approval No: NaMoMC/IRB/2024/Dissertation/145, dated 24/07/2024). Written informed consent was obtained from all participants prior to enrollment in English, Gujarati, or Hindi as appropriate. Patient confidentiality was strictly maintained throughout.

RESULTS

Demographic, nutritional, and socioeconomic profile

A total of 100 adult patients with drug-resistant tuberculosis were enrolled and followed up throughout their treatment course. Demographics and baseline characteristics are summarized in Table I. The study population demonstrated a marked male predominance, with 63 patients (63%) being male and 37 (37%) female (male-to-female ratio 1.7:1). The mean age of participants was 36.8 years (range 15–72 years). The majority of patients belonged to economically productive age groups: 38% were aged 15–30 years and 34% were aged 31–45 years, while 25% were aged 46–60 years and only 3% were older than 60 years.

Undernutrition was strikingly prevalent: 84 patients (84%) were underweight at baseline (BMI <18.5 kg/m²), 9% had a normal BMI (18.5–22.9 kg/m²), 2% were pre-obese (23.0–24.9 kg/m²), and 5% were obese (grade I or II). According to the Modified Kuppuswamy scale, 78% of patients belonged to the lower socioeconomic class, 10% to the middle class, and 12% to upper-middle or higher strata. Among underweight individuals, 74 (88.1%) belonged to the lower socioeconomic class.

Clinical presentation and baseline comorbidities

Cough was the most frequent presenting symptom, reported by 99% of patients, followed by anorexia (83%), weight loss (76%), fever (58%), dyspnea (53%), chest pain (42%), malaise (42%), and hemoptysis (14%). Miscellaneous symptoms including abdominal pain, arthralgia, myalgia, weakness, and back pain were reported by 16% of patients.

Baseline comorbidities were identified in 31 patients (31%). Diabetes mellitus was the commonest co-existing condition, observed in 10% of patients as isolated DM, and in combination with hypertension (1%), hypothyroidism (2%), and ischemic heart disease (3%). Other comorbidities included isolated hypertension (7%), chronic obstructive pulmonary disease (COPD, 3%), people living with HIV/AIDS (PLHA, 2%), asthma (1%), seizure disorder (1%), and post-TB obstructive airway disease (1%).

Distribution of treatment regimens

The distribution of prescribed DR-TB treatment regimens is presented in Table II. The longer all-oral MDR/RR-TB regimen was prescribed in the majority of patients (69%), reflecting NTEP recommendations for complex MDR, pre-XDR, and fluoroquinolone-resistant cases. The all-oral BPaLM regimen was utilized in 20% of patients, representing its recent programmatic rollout. Shorter oral MDR/RR-TB regimens were administered to 8% of patients, while isoniazid mono/poly-DR-TB (Hr-TB) regimens accounted for 3% of cases.

Spectrum, severity, and temporal onset of adverse drug reactions

All 100 enrolled patients (100%) experienced at least one adverse drug reaction during their treatment course. The overall severity distribution demonstrated that mild ADRs (Grade 1) predominated, occurring in 65% of patients. Moderate ADRs (Grade 2) were observed in 20% of patients, while severe ADRs (Grade 3–4) occurred in 15% of patients (Table III).

Regarding the temporal pattern of ADR onset, 31% of reactions occurred within the first month of treatment (<1 month, early-onset), 10% developed between 1 and 2 months (intermediate-onset), and 59% manifested after 2 months (>2 months, late-onset). Early-onset ADRs (<1 month) were predominantly mild (24/31, 77.4%), though 5 severe reactions occurred during this initial phase. Late-onset ADRs (>2 months) accounted for the largest proportion of moderate (15/20, 75.0%) and severe (9/15, 60.0%) reactions, reflecting cumulative drug exposure.

Specific ADR types and management interventions

The detailed clinical spectrum, suspected causative agents, mean onset timing, severity breakdown, and management interventions for specific ADRs are summarized in Table III:

- Peripheral Neuropathy: The single most frequent ADR overall, occurring in 43 patients (43%; 19 mild, 14 moderate, 10 severe) with a mean onset of 2.78 months. It was primarily associated with linezolid and cycloserine exposure. Severe cases (n=10) required linezolid discontinuation and replacement with ethambutol; moderate cases (n=14) were managed by reducing linezolid dosage from 600 mg to 300 mg daily; mild cases

received symptomatic support with pyridoxine and amitriptyline.

- Skin Discoloration: Reported in 42 patients (42%; 32 mild, 10 moderate, 0 severe) with a mean onset of 2.91 months, directly attributable to clofazimine skin pigmentation. All patients were successfully managed with clinical reassurance.
- Gastritis & Gastrointestinal Distress: Observed in 18 patients (18%, all mild) with a mean onset of 2.79 months, caused by ethionamide, PAS, pyrazinamide, linezolid, and fluoroquinolones. Symptoms responded to H2-blockers, proton pump inhibitors, and taking medications with food. In severe gastritis, temporary regimen hold for up to 5 days was effective.
- Arthralgia: Developed in 7 patients (7%, all mild) with an early mean onset of 20 days, linked to pyrazinamide-induced hyperuricemia, fluoroquinolones, and bedaquiline. Managed with short courses of NSAIDs (ibuprofen).
- Hepatotoxicity: Documented in 6 patients (6%; 5 mild, 1 moderate) with a mean onset of 30 days, suspected due to pyrazinamide, isoniazid, ethionamide, or bedaquiline. Moderate hepatotoxicity required withholding bedaquiline and hepatotoxic drugs for 5 days until transaminases declined below 2x ULN, followed by stepwise reintroduction.
- Nephrotoxicity: Occurred in 4 patients (4%; 2 mild, 2 moderate) with a mean onset of 2.0 months, associated with cycloserine and injectable history. Managed by cycloserine dose reduction and renal function monitoring.
- Alopecia: Noted in 3 patients (3%, all mild) with a mean onset of 3.0 months, attributed to ethionamide. Managed with reassurance.
- Optic Neuropathy: Developed in 2 patients (2%; 1 moderate, 1 severe) at a mean onset of 4.0 months, caused by linezolid and ethionamide. Required permanent linezolid/ethionamide withdrawal and substitution with pyrazinamide/ethambutol after ophthalmological confirmation.
- Allergic Skin Reactions: Observed in 2 patients (2%, both moderate) with an early mean onset of 15 days. Managed with antihistamines and gradual drug rechallenge.
- Psychiatric Symptoms: Occurred in 2 patients (2%; 1 moderate, 1 severe) with a mean onset of 3.0 months, caused by cycloserine central neurotoxicity. Managed by temporary cycloserine hold (2 weeks) in moderate cases, and permanent withdrawal in severe cases.
- Diarrhea: Reported in 2 patients (2%, both mild) at 20 days, managed with racecadotril and oral rehydration.
- Cardiac ADRs (VPCs / QTc Prolongation): Observed in 2 patients (2%; 1 moderate, 1 severe) at a mean onset of 2.5 months following bedaquiline and clofazimine therapy. Bedaquiline was permanently discontinued and substituted with delamanid, while clofazimine was withheld for 15 days.
- Myelosuppression: Reported in 1 patient (1%, severe anemia/thrombocytopenia) at 1 month due to linezolid toxicity, managed by linezolid dose reduction to 300 mg daily and supportive transfusion.
- Seizures: Occurred in 1 patient (1%, severe) at 5 months due to cycloserine neurotoxicity. Managed by permanent cycloserine withdrawal, anticonvulsant therapy, and substitution with pyrazinamide.

Association between body mass index and ADR severity

To evaluate whether nutritional status influenced ADR severity, patients were cross-tabulated into underweight (BMI <18.5 kg/m², n=84) and normal/overweight (BMI ≥18.5 kg/m², n=16) groups against mild versus moderate/severe ADR outcomes. Among underweight patients, 55 (65.5%) experienced mild ADRs and 29 (34.5%) experienced moderate-to-severe ADRs. Among normal/overweight patients, 10 (62.5%) experienced mild ADRs and 6 (37.5%) experienced moderate-to-severe ADRs. Fisher's exact test demonstrated an odds ratio of 1.14 (95% CI: 0.37–3.48, p = 1.00), indicating no statistically significant association between baseline BMI category and ADR severity in this cohort.

Management interventions and final treatment outcomes

Overall, management of ADRs relied predominantly on protocolized conservative measures: drug hold and rechallenge was successfully executed in 85 patients (85%), drug modification (dose reduction) was performed in 11 patients (11%), and permanent drug withdrawal with substitution was required in 4 patients (4%) (Table IV).

Final treatment outcomes for the entire cohort of 100 patients demonstrated an overall treatment success rate of 91.0% (95% CI: 83.6–95.8%), comprising 80 patients (80%) declared cured and 11 patients (11%) who completed treatment. Unfavorable outcomes occurred in 9 patients: 6 (6%) were lost to follow-up, 2 (2%) died during treatment, and 1 (1%) experienced treatment failure.

Among the 85 patients managed with drug hold and rechallenge, 68 (80.0%) were cured, 11 (12.9%) completed treatment, 2 (2.4%) died, and 4 (4.7%) were lost to follow-up. Among the 11 patients requiring drug modification, 9 (81.8%) were cured and 2 (18.2%) were lost to follow-up, with zero deaths or failures. Among the 4 patients requiring permanent drug withdrawal, 3 (75.0%) achieved cure, while 1 patient (25.0%) experienced treatment failure.

The single treatment failure occurred in a patient initiated on the BPaLM regimen who developed severe Grade 4 linezolid-induced peripheral neuropathy within the initial 9 weeks of therapy.

Permanent discontinuation of linezolid rendered the short-course BPaLM regimen non-viable; as per NTEP guidelines, the patient was declared a treatment failure and transitioned to an individualized longer all-oral MDR-TB regimen.

Table 1:Demographic and baseline clinical characteristics of the study participants (N=100)

Characteristic	Category / Parameter	n (%)
Sex	Male	63 (63.0)
	Female	37 (37.0)
Age group (yr)	18–30	38 (38.0)
	31–45	34 (34.0)
	46–60	25 (25.0)
	>60	3 (3.0)
Body Mass Index (BMI)	Underweight (<18.5 kg/m²)	84 (84.0)
	Normal range (18.5–22.9 kg/m²)	9 (9.0)
	Pre-obese (23.0–24.9 kg/m²)	2 (2.0)
	Obese Class I (25.0–29.9 kg/m²)	3 (3.0)
	Obese Class II (≥30.0 kg/m²)	2 (2.0)
Socioeconomic status*	Lower class	78 (78.0)
	Middle class	10 (10.0)
	Upper-middle / Higher class	12 (12.0)
Presenting symptoms	Cough	99 (99.0)
	Anorexia	83 (83.0)
	Weight loss	76 (76.0)
	Fever	58 (58.0)
	Dyspnea	53 (53.0)
	Chest pain	42 (42.0)
	Malaise	42 (42.0)
	Hemoptysis	14 (14.0)
Comorbidities	None	69 (69.0)
	Diabetes mellitus (DM)	10 (10.0)
	Hypertension (HTN)	7 (7.0)
	Ischemic heart disease & DM	3 (3.0)
	COPD	3 (3.0)
	Hypothyroidism & DM	2 (2.0)
	People living with HIV (PLHA)	2 (2.0)
	Asthma / Seizure / Post-TB OAD / DM+HTN	4 (4.0)

Categorized according to the Modified Kuppuswamy socioeconomic scale.

Table 2: Distribution of drug-resistant tuberculosis treatment regimens (N=100)

Treatment Regimen	Prescribed Drugs & Duration	n (%)
Longer Oral MDR/RR-TB Regimen	(18–20 m) Bdq (6m+), Lfx, Lzd, Cfz, Cs	69 (69.0)
BPaLM Regimen	(26–39 w) Bdq, Pa, Lzd (600/300mg), Mfx	20 (20.0)
Shorter Oral MDR/RR-TB Regimen	(9–11 m) Bdq (6m), Lfx, Cfz, Z, E, Hh, Lzd	8 (8.0)
Isoniazid mono/poly DR-TB Regimen	(6–9 m) Lfx, R, E, Z	3 (3.0)
Total	--	**100 (100.0)**

Table 3: Spectrum, severity breakdown, onset timing, causative agents, and management of adverse drug reactions (N=100)

Adverse Drug Reaction	Total n (%)	Mild n (%)	Mod n (%)	Sev n (%)	Mean Onset	Offending Drug(s)	Primary Management Intervention
Peripheral neuropathy	43 (43.0)	19 (44.2)	14 (32.6)	10 (23.3)	2.78 m	Lzd, Cs, Hh	Stop Lzd + add E (severe); Lzd 300mg (mod); Pyridoxine (mild)
Skin discoloration	42 (42.0)	32 (76.2)	10 (23.8)	0 (0.0)	2.91 m	Cfz	Patient counseling and reassurance
Gastritis & GI distress	18 (18.0)	18 (100.0)	0 (0.0)	0 (0.0)	2.79 m	PAS, Eto, Z, Lzd	PPIs/H2 blockers; hold regimen 5 days if severe
Arthralgia	7 (7.0)	7 (100.0)	0 (0.0)	0 (0.0)	20 days	Z, FQ, Bdq	Symptomatic treatment (NSAIDs / Ibuprofen)
Hepatotoxicity	6 (6.0)	5 (83.3)	1 (16.7)	0 (0.0)	30 days	Z, H, R, Eto, Bdq	Hold Bdq/hepatotoxic drugs 5 days; restart after LFT recovery
Nephrotoxicity	4 (4.0)	2 (50.0)	2 (50.0)	0 (0.0)	2.0 m	Cs, Am	Dose reduction of Cycloserine; RFT monitoring
Alopecia	3 (3.0)	3 (100.0)	0 (0.0)	0 (0.0)	3.0 m	Eto	Patient counseling and reassurance
Optic neuropathy	2 (2.0)	0 (0.0)	1 (50.0)	1 (50.0)	4.0 m	Lzd, Eto, E	Stop Lzd/Eto permanently; initiate Pyrazinamide/Ethambutol

Allergic skin reaction	2 (2.0)	0 (0.0)	2 (100.0)	0 (0.0)	15 days	Any agent	Antihistamines; stepwise rechallenge
Psychiatric symptoms	2 (2.0)	0 (0.0)	1 (50.0)	1 (50.0)	3.0 m	Cs, FQ, Hh	Hold Cs 2 weeks (moderate); permanent stop Cs (severe)
Diarrhea	2 (2.0)	2 (100.0)	0 (0.0)	0 (0.0)	20 days	PAS, Eto	Symptomatic treatment (Racecadotril)
Cardiac (QTc / VPCs)	2 (2.0)	0 (0.0)	1 (50.0)	1 (50.0)	2.5 m	Bdq, Cfz, FQ	Stop Bdq permanently + start Delamanid; hold Cfz 15 days
Myelosuppression	1 (1.0)	0 (0.0)	0 (0.0)	1 (100.0)	1.0 m	Lzd	Lzd dose reduction to 300mg / temporary hold; transfusion
Seizure	1 (1.0)	0 (0.0)	0 (0.0)	1 (100.0)	5.0 m	Cs, Hh, FQ	Stop Cs permanently; start Pyrazinamide + anticonvulsants

Table 4: Final treatment outcomes according to adverse drug reaction management strategy (N=100)

ADR Management Strategy	n (%)	Cured n (%)	Completed n (%)	Success n (%)	Lost to Follow-up n (%)	Died n (%)	Failed n (%)
Drug Hold &Rechallenge	85 (85.0)	68 (80.0)	11 (12.9)	79 (92.9)	4 (4.7)	2 (2.4)	0 (0.0)
Drug Modification (Dose Reduction)	11 (11.0)	9 (81.8)	0 (0.0)	9 (81.8)	2 (18.2)	0 (0.0)	0 (0.0)
Permanent Drug Withdrawal	4 (4.0)	3 (75.0)	0 (0.0)	3 (75.0)	0 (0.0)	0 (0.0)	1 (25.0)
Total Cohort	**100 (100.0)**	**80 (80.0)**	**11 (11.0)**	**91 (91.0)**	**6 (6.0)**	**2 (2.0)**	**1 (1.0)**

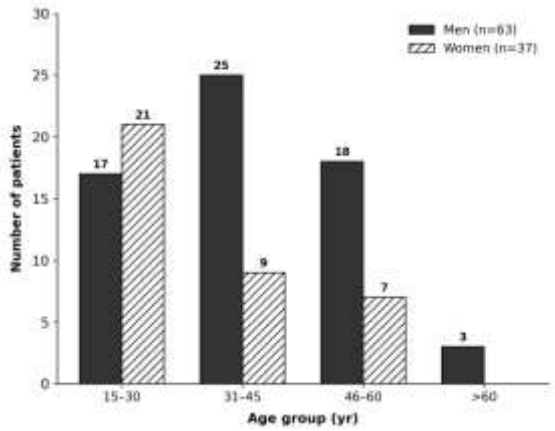

Figure 1: Age and sex distribution of the 100 patients with drug-resistant tuberculosis undergoing treatment under NTEP. Bars illustrate patient counts across age brackets (15–30, 31–45, 46–60, and >60 yr) stratified by sex

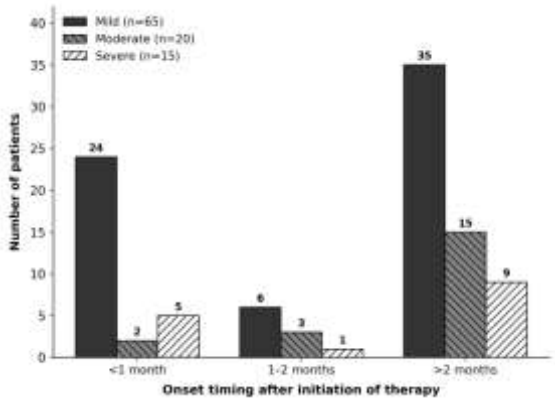

Figure 2: Distribution of adverse drug reaction (ADR) severity (mild, moderate, severe) stratified by onset timing (<1 month, 1–2 months, and >2 months) following initiation of DR-TB treatment

DISCUSSION

This prospective observational study provides critical real-world evidence regarding the spectrum, severity, onset timing, management, and treatment outcomes of adverse drug reactions among patients receiving standardized all-oral DR-TB regimens under the National Tuberculosis Elimination Programme (NTEP) at a tertiary care center in Western India.[3,4,10,20,22] Key findings demonstrate that while ADRs were universal (100%), the vast majority (85%) were mild-to-moderate and manageable through structured aDSM protocols without compromising high overall treatment success (91%). The demographic profile of our cohort—characterized by a 63% male predominance and 72% clustering in the economically productive age group of 15–45 years—aligns closely with established Indian and international DR-TB literature. Indian studies by Swapnil Jain et al. (73.2% male),[12] O.P. Giri et al. (75.7% male),[13] and Vishakha et al. (59.8% male) similarly demonstrate male vulnerability, which may reflect heightened environmental exposure, higher tobacco/alcohol usage, and distinct healthcare-seeking behaviors. Furthermore, 84% of our patients were underweight at baseline and 78% belonged to lower socioeconomic strata, mirroring data from Swapnil Jain et al. (88.6% underweight)[12] and Sumankumar et al. (74.8% underweight). Undernutrition and poverty create a synergistic bidirectional complex with TB, impairing cell-mediated immunity, altering drug pharmacokinetics through hypoproteinemia, and enhancing susceptibility to drug toxicity.

The distribution of treatment regimens in our study reflects the ongoing programmatic transition under NTEP. Longer all-oral MDR/RR-TB regimens remained the mainstay (69%), consistent with WHO

Global TB Report 2025 India subsets (60–65%)[1,2,4] and Indian cohorts by Gupta et al. (70%),[21] Patel et al. (68%),[22] and Udwadia et al. (62%).[20] The high utilization of longer oral regimens in real-world Indian settings is driven by high baseline fluoroquinolone resistance, extensive/cavitary parenchymal involvement, and prior second-line drug exposure. Concurrently, the BPaLM regimen accounted for 20% of prescriptions, matching rates reported by Udwadia et al. (22%)[20] and Patel et al. (19%),[22] underscoring growing programmatic confidence in shorter, highly effective 6-month all-oral regimens.

In our study, 59% of ADRs manifested after 2 months of therapy, demonstrating a clear predominance of late-onset cumulative toxicity. This observation is consistent with aDSM data from the India TB Report 2025[2] and international cohorts by Borisov et al.[10] and Sotgiu et al.,[11] where late-onset ADRs accounted for 55–60% of toxicities. Cumulative drug exposure to linezolid, clofazimine, bedaquiline, and cycloserine drives progressive organ stress, mitochondrial injury, and tissue accumulation over time. However, 31% of ADRs occurred within the first month, including 5 severe reactions (myelosuppression, early neuropathy, allergic reactions). This bimodal temporal pattern underscores that while routine monthly monitoring is vital for late cumulative toxicities, intensive biweekly monitoring during the initial 30 days is crucial to detect acute, life-threatening reactions early.

Neurological toxicities constituted the most clinically significant ADR category. Peripheral neuropathy occurred in 43% of patients, representing the single most common severe ADR. This high frequency is directly attributable to the core role of linezolid (600 mg daily) and cycloserine in longer oral and BPaLM regimens. Linezolid inhibits mitochondrial protein synthesis, causing axonal degeneration, particularly after 8–12 weeks of cumulative administration. Our neuropathy incidence (43%) is comparable to reports by Swapnil Jain et al. (38%),[12] Omer et al. (34%),[15] and Joohae Kim et al. (41%). Crucially, 14 moderate cases were successfully managed by reducing linezolid dosage to 300 mg daily, and 19 mild cases responded to symptomatic support, preserving regimen integrity. Permanent withdrawal was required in only 10 severe cases. Optic neuropathy (2%) and seizures (1%) were less frequent but represented severe, treatment-modifying events requiring immediate drug withdrawal and expert substitution.

Dermatological ADRs were dominated by clofazimine-induced skin discoloration (42%), resulting from lipophilic drug accumulation in dermal macrophages.[10,23] While benign and non-progressive, skin pigmentation carries immense psychosocial stigma; all 42 patients were managed with empathetic counseling and reassurance. Gastrointestinal toxicities (gastritis 18%, diarrhea 2%) were frequent but predominantly mild, responding well to antacids, PPIs, and taking drugs with food—a lower incidence than older injectable-era studies (26–28%)[16,18,19,23] owing to better supportive care protocols.

Systemic toxicities—including hepatotoxicity (6%), nephrotoxicity (4%), arthralgia (7%), and cardiotoxicity (2%)—were markedly lower than in historical injectable-based cohorts.[13,16,18,19] Older studies by Giri et al. and Kim et al. reported nephrotoxicity rates of 7–12% due to aminoglycoside-induced acute tubular necrosis. The shift to all-oral regimens has largely eliminated permanent renal failure and ototoxicity. Similarly, cardiotoxicity (QTc prolongation/VPCs) was restricted to 2% of patients despite concurrent bedaquiline and clofazimine use, reflecting strict baseline screening and routine ECG monitoring.

Management of ADRs using standardized NTEP algorithms proved highly effective. Rechallenge after temporary drug hold (85%) and dose modification (11%) allowed 96% of patients to continue their primary regimen.[3,4,10,20,22] Permanent drug withdrawal was necessary in only 4% of cases. Consequently, our cohort achieved an overall treatment success rate of 91% (80% cured, 11% completed), outperforming national programmatic benchmarks (70–75%)[2,4] and global averages reported in the WHO Global TB Report 2025 (68–72%).[1] Mortality (2%) and treatment failure (1%) were exceptionally low compared to Indian literature (mortality 6–8%, failure 3–4%).[17,18,19,20,24,25]

The single treatment failure in our cohort highlights an important programmatic vulnerability of shorter regimens such as BPaLM. When severe Grade 4 linezolid toxicity necessitates permanent drug withdrawal during the first 9 weeks, the BPaLM regimen loses a key bactericidal component without provision for within-regimen substitution. As mandated by guidelines, such patients must be declared treatment failures and transitioned to longer all-oral regimens, underscoring the rigid eligibility constraints of short-course regimens.[4,9]

Strengths of this study include its prospective design, protocolizedaDSM schedule, complete patient follow-up, and precise management documentation under real-world NTEP conditions. Limitations include the single-center setting, a modest sample size (N=100) which limits detection of rare ADRs, lack of an unexposed control group, and descriptive statistical design. Furthermore, serum drug concentration monitoring was not available.

CONCLUSION

In conclusion, adverse drug reactions are universal among DR-TB patients receiving modern all-oral NTEP regimens, but are predominantly mild-to-moderate and manageable through structured aDSM protocols. Protocolized drug hold, rechallenge, and dose reduction effectively preserve regimen continuity, yielding excellent treatment success (91%). Strengthening active pharmacovigilance,

nutritional support, and timely ADR management is vital to optimizing patient outcomes and advancing India's national goal of eliminating tuberculosis.

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