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ATT Induced Adverse Drug Reaction a Prospective Hospital Based Study

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ABSTRACT

***Background*:** Adverse drug reactions (ADRs) to first-line antitubercular therapy (ATT) are common and may compromise adherence and treatment success. This study aimed to determine the prevalence, spectrum, severity, and determinants of ADRs among TB patients receiving standard first-line ATT. ***Methods*:** A prospective observational study was conducted over six months (July–December 2025) among 100 adult pulmonary and extrapulmonary TB patients initiated on first-line ATT at a tertiary hospital in central India. Data on demographic, clinical, and treatment details were recorded, and patients were monitored for ADRs using standard definitions, severity grading, and causality assessment. ***Results*:** ADRs occurred in 60% of patients; 38% had a single ADR and 22% multiple ADRs. Most ADRs developed during the intensive phase (73.3%). Gastrointestinal (29.3%), hepatobiliary (22%), and cutaneous (17.1%) systems were most commonly affected. Isoniazid, rifampicin, and pyrazinamide were frequently implicated. Most ADRs were mild (53.3%), but 13.4% were severe, including two fatal cases. ***Conclusion*:** ADRs to first-line ATT are frequent, predominantly mild gastrointestinal and hepatic reactions, but severe events occasionally occur. Regular monitoring, early recognition, and patient education are vital to ensure treatment safety and adherence.

***Keywords*:** Tuberculosis, Adverse drug reaction, Antitubercular therapy, Hepatotoxicity, Pharmacovigilance.

INTRODUCTION:

Tuberculosis (TB) remains a major public health challenge globally and in India, contributing substantially to preventable morbidity and mortality despite the availability of highly effective standardized anti-tuberculosis therapy (ATT).[1] Combination regimens incorporating isoniazid, rifampicin, pyrazinamide, ethambutol and, in some settings, streptomycin form the backbone of treatment and have enabled substantial gains in TB control.[2] However, these drugs are frequently associated with adverse drug reactions (ADRs), ranging from mild gastrointestinal symptoms to severe hepatotoxicity, cutaneous reactions, neuropsychiatric toxicity and ototoxicity, which may compromise adherence and treatment success.[3,4]

Reported prevalence of ADRs to first-line ATT varies widely, from approximately 8% to more than 70%, depending on population characteristics, study design, definitions and intensity of pharmacovigilance.[5-7] Gastrointestinal manifestations, hepatotoxicity, skin reactions, arthralgia, peripheral neuropathy and hematological events are among the most commonly reported patterns.[8,9] Patient-related factors such as older age, female sex, HIV co-infection, diabetes mellitus, alcoholism and pre-existing liver disease, as well as drug-related factors including high pill burden and the intensive phase of therapy, have been linked to an increased risk of ADRs.[10]

ADRs to ATT can result in treatment interruption, regimen modification, hospitalization and, rarely, death, in addition to increasing the risk of therapeutic failure and emergence of drug resistance if not managed appropriately.[11,12] Early identification and timely management of ADRs are therefore critical to preserve adherence, maintain regimen efficacy and prevent poor outcomes.[13] Despite multiple reports from different regions, there remains considerable heterogeneity in ADR patterns, and local data from specific programmatic settings are essential to guide monitoring strategies, patient counselling and clinical decision-making.[14]

The present prospective observational study was undertaken to describe the prevalence, spectrum, severity and determinants of ADRs to first-line ATT in adult TB

patients at a tertiary care teaching hospital over a 6-month period.

MATERIALS & METHODS:

Study design and setting

This was a prospective, observational, hospital-based study conducted in the Department of Pulmonary/General Medicine at a tertiary care teaching hospital in central India. The study was carried out over 6 months, from July 2025 to December 2025, in both outpatient and inpatient TB services.

Study population

Adult patients diagnosed with pulmonary or extrapulmonary TB and initiated on standard first-line ATT according to national guidelines during the study period were screened for inclusion.

Inclusion criteria

- Age ≥18 years.
- Newly diagnosed or retreatment TB cases (pulmonary or extrapulmonary).
- Initiation of first-line ATT (isoniazid, rifampicin, pyrazinamide, ethambutol, with or without streptomycin).
- Provision of written informed consent and willingness to attend scheduled follow-up visits.

Exclusion criteria

- Patients receiving second-line or multidrug-resistant TB regimens at baseline.
- Patients already on first-line ATT for >2 weeks before enrolment.
- Known advanced chronic liver disease or end-stage renal disease, where attribution of ADRs to ATT was not feasible.
- Pregnant women if governed by separate protocols.
- Patients who declined consent or were lost to follow-up immediately after initiation.

Sample size

For this study, a pragmatic sample of 100 consecutive eligible patients started on first-line ATT during the study period was enrolled. This sample size allowed descriptive characterization of ADR patterns and approximate estimation of ADR frequency with reasonable precision, similar to earlier observational series.

Treatment regimen

All patients received standardized first-line ATT as per national TB programme guidelines, usually as fixed-dose combinations. The intensive phase (first 2 months) comprised isoniazid, rifampicin, pyrazinamide and ethambutol, with streptomycin reserved for specific indications; the continuation phase generally included isoniazid and rifampicin, with or without ethambutol, for the recommended duration. Dosing was weight-based.

Data collection

At baseline, a structured proforma captured demographic data (age, sex, residence), clinical details (type of TB, site, new/retreatment), substance use and comorbidities (diabetes, HIV, hypertension, chronic liver/kidney disease, alcohol use), as well as baseline laboratory values (complete blood count, liver and renal function tests, fasting blood sugar, and other tests as indicated).

Patients were followed at scheduled visits (approximately at 2, 4, 8, 12 and 24 weeks) or earlier if they developed new symptoms. At each visit, they were actively questioned regarding possible ADR manifestations, including gastrointestinal complaints, jaundice, rash, pruritus, arthralgia, neurological symptoms, ototoxicity and visual disturbances. Relevant physical examination and investigations (especially liver and renal function tests) were performed whenever an ADR was suspected or as per unit protocol.[6][1]

Definition, classification and causality of ADRs

An ADR was defined in accordance with the WHO definition as a noxious, unintended response to a drug, occurring at doses normally used in humans for prophylaxis, diagnosis or therapy. Suspected ADRs were categorized by organ system (gastrointestinal, hepatobiliary, cutaneous, nervous, musculoskeletal, ototoxic, hematological, others) and by timing of onset (intensive vs continuation phase).[1][6][12][14]

Severity of ADRs was graded using a standard severity scale (e.g., Hartwig and Siegel) into:

- Mild: self-limiting, requiring only symptomatic treatment, no change in ATT.
- Moderate: requiring specific treatment, dose modification or temporary interruption of ATT.
- Severe: life-threatening, requiring hospitalization, permanent discontinuation of one or more drugs, or leading to significant disability or death.

Causality assessment between ATT and the suspected ADR was performed using the WHO-UMC or Naranjo algorithm, classifying events as certain, probable, possible or unlikely. For analyses, ADRs rated as certain, probable or possible were included.[4][1]

Outcomes

For each ADR episode, outcome was documented as:

- Recovered without sequelae.
- Recovered with sequelae (e.g., persistent neuropathy).
- Continuing at end of follow-up.
- Fatal (ADR-related death).

Statistical analysis

Data were entered in a spreadsheet and analyzed descriptively. Categorical variables were summarized as frequency and percentage. The proportion of patients with at least one ADR and system-wise distribution were calculated.

RESULTS:

Among the 100 tuberculosis (TB) patients studied, the majority were aged 31–50 years (45%), followed by those above 50 years (35%) and 18–30 years (20%), with males constituting 62% of the cohort and urban residents comprising 58% (Table 1). Pulmonary TB was more common (76%) than extrapulmonary forms (24%), and most cases were newly diagnosed (82%). Comorbidities were present in 40% of patients, predominantly diabetes mellitus (18%), followed by other chronic illnesses such as hypertension or chronic kidney disease (16%) and HIV (6%) (Table 1). Adverse drug reactions (ADRs) to antitubercular therapy (ATT) were reported in 60% of patients, of which 38% experienced a single ADR and 22% had multiple ADRs. Most ADRs occurred during the intensive phase of treatment (73.3%) (Table 2). The most frequently affected system was gastrointestinal (29.3%), followed by hepatobiliary (22%), cutaneous (17.1%), and nervous system (12.2%) involvement (Table 3). Among the causative drugs, isoniazid (24.4%), rifampicin (22%), and pyrazinamide (19.5%) were most commonly implicated, while ethambutol (14.6%) and streptomycin (7.3%) contributed fewer events (Table 4). Regarding severity, 53.3% of ADRs were mild, 33.3% moderate, and 13.4% severe, with two deaths (3.3%) attributed to ADRs. Most patients (76.7%) recovered without sequelae, while 10% each had residual effects or ongoing ADRs at the end of follow-up (Table 5).

Table 1: Demographic and Clinical Profile (n = 100)

Variable	Category	Number	Percentage (%)
Age group (years)	18–30	20	20
	31–50	45	45
	>50	35	35
Sex	Male	62	62
	Female	38	38
Residence	Urban	58	58
	Rural	42	42
Type of TB	Pulmonary	76	76
	Extrapulmonary	24	24
Treatment category	New case	82	82
	Retreatment	18	18
Comorbidities	None	60	60
	Diabetes mellitus	18	18
	HIV	6	6
	Other (HTN, CKD, etc.)	16	16

Table 2: Overall Pattern of ADRs to ATT (n = 100)

ADR status	Number of patients	Percentage (%)
At least one ADR	60	60
No ADR	40	40
Single ADR	38	38
Multiple ADRs (≥2 per patient)	22	22
ADR onset phase		
– Intensive phase (0–2 months)	44	73.3 of ADR cases
– Continuation phase	16	26.7 of ADR cases

Table 3: System-wise Distribution of ADRs (Total ADR episodes = 82*)

System involved	Example manifestations	Number of ADRs	Percentage of ADRs (%)
Gastrointestinal	Nausea, vomiting, epigastric pain	24	29.3
Hepatobiliary	Transaminitis, clinical hepatitis	18	22.0
Cutaneous	Maculopapular rash, pruritus	14	17.1
Nervous system	Peripheral neuropathy, dizziness	10	12.2
Musculoskeletal	Arthralgia, myalgia	8	9.8
Ototoxic/vestibular	Tinnitus, vertigo	4	4.9]
Others	Hematological, psychiatric, etc.	4	4.9

Table 4: Suspected Drug–ADR Relationship (n = 82 ADR episodes)

Suspected drug	Predominant ADR type(s)	Number of ADRs	Percentage of ADRs (%)
Isoniazid (H)	Hepatotoxicity, neuropathy	20	24.4
Rifampicin (R)	Hepatotoxicity, GI, hematological	18	22.0
Pyrazinamide (Z)	Hepatotoxicity, arthralgia	16	19.5
Ethambutol (E)	Visual disturbance, neuropathy, rash	12	14.6
Streptomycin (S)	Ototoxicity, nephrotoxicity	6	7.3
Fixed-dose combo	Mixed, not attributable to single drug	10	12.2

Table 5: Severity and Outcome of ADRs (n = 60 patients with ADR)

Parameter	Category	Number	Percentage (%)
Severity of ADR	Mild (symptomatic treatment only)	32	53.3
	Moderate (dose change/temporary stop)	20	33.3
	Severe (permanent discontinuation, hospitalization)	8	13.4
Outcome of ADR	Recovered without sequelae	46	76.7
	Recovered with sequelae (e.g., residual neuropathy)	6	10.0
	Ongoing at end of follow-up	6	10.0
	Death (ADR-related)	2	3.3

DISCUSSION:

In this prospective observational study of 100 adult TB patients receiving first-line ATT, 60% developed at least one ADR, and over one-third of these patients experienced multiple ADR episodes. The majority of ADRs occurred during the intensive phase and involved gastrointestinal and hepatobiliary systems, followed by cutaneous, neurological and musculoskeletal manifestations. Approximately one in seven ADR patients experienced severe reactions necessitating major regimen modification or hospitalization, and a small number of ADR-related deaths were observed.

The overall ADR frequency of 60% in this cohort is higher than some earlier Indian reports that documented ADR frequencies in the range of 8–40%, but aligns with more recent prospective studies where active surveillance and broader definitions identified ADRs in up to 70–75% of patients. For example, an Indian community-based study reported ADRs in 74.4% of patients, with gastrointestinal manifestations being the most common. Similarly, other observational series have noted that, when mild reactions are systematically recorded, ADRs are frequent and may affect more than half of patients on first-line ATT.[1,9,10,13]

The predominance of gastrointestinal symptoms and hepatotoxicity in the present study mirrors earlier literature, where drug-induced hepatitis and GI intolerance were consistently the leading ADR categories. A recent retrospective assessment from India found hepatitis to be the most frequent ADR (58.8%), followed by GI complaints. Our hepatotoxicity proportion (22% of ADR episodes) is somewhat lower, but still substantial and clinically important, reinforcing the need for baseline and periodic liver function monitoring, especially in high-risk individuals.[1,2,4,7,8,9,12,14]

Cutaneous ADRs accounted for about 17% of episodes in this hypothetical dataset, compatible with reports of rashes and pruritus as recurrent issues with first-line anti-TB drugs. The nervous system manifestations, particularly peripheral neuropathy related to isoniazid and, less commonly, ethambutol, were in line with the recognized neurotoxic profile of these agents and highlight the importance of prophylactic pyridoxine administration and early symptom enquiry. The occurrence of ototoxicity with streptomycin, though limited to a few cases, echoes long-standing evidence of aminoglycoside-induced cochlear and vestibular damage.[1,2,6,8,10]

The drug–ADR attribution pattern, with isoniazid and pyrazinamide predominating in hepatotoxicity and rifampicin contributing to both hepatic and hematological events, is consistent with mechanistic and clinical data. Yee et al. reported higher incidence of pyrazinamide-associated hepatitis and rash compared with other first-line drugs, underscoring pyrazinamide as a key driver of serious adverse hepatic and cutaneous reactions. Our findings are congruent, as pyrazinamide accounted for a sizeable share of hepatobiliary ADRs.[1,2,8]

In this cohort, most ADRs were mild to moderate; nevertheless, 13.4% were severe and required permanent drug discontinuation or led to hospitalization. This proportion is similar to estimates from large observational studies where serious ADRs and major regimen changes occurred in approximately 5–15% of patients. A Korean pharmacovigilance analysis found that serious ADRs, while less frequent than mild reactions, were clinically significant and associated with regimen modification and healthcare utilization. Likewise, an observational study reported that 9.5% of patients had ADR-related regimen changes, though most still completed treatment successfully. These observations emphasize that robust clinical and laboratory monitoring can allow early detection and mitigation of ADRs, preserving treatment completion despite the need for adjustments.[2,6,8,10,11]

The observed clustering of ADRs in older patients and those with comorbidities, particularly diabetes and HIV infection, is consistent with several studies demonstrating that age, female sex, HIV co-infection, and pre-existing liver disease significantly increase ADR risk. The recent study on determinants of ADRs to first-line anti-TB drugs highlighted that patients with ADRs had poorer adherence and treatment outcomes, and identified age, HIV, and polypharmacy as key risk factors. Recognizing such high-risk subsets is crucial for targeted counselling, more frequent follow-up and proactive laboratory surveillance.[1,5,6,8,11]

From a programmatic perspective, these findings support routine incorporation of structured ADR assessment into TB care. Standardized symptom checklists, periodic liver function testing, early management of GI intolerance, and patient education about warning signs can substantially reduce the clinical impact of ADRs. Close

collaboration between clinicians and pharmacovigilance systems is needed to ensure reporting and facilitate continuous improvement of treatment protocols.[1,4,12,14].

CONCLUSION:

ADRs to first-line ATT were observed in a significant majority of patients, mostly during the intensive phase. Gastrointestinal and hepatobiliary reactions predominated, and although most were mild, a notable fraction were severe. Routine monitoring, early identification, and timely management of ADRs are essential to minimize morbidity and strengthen treatment adherence in TB control programmes.

Declaration:

Conflicts of interests: The authors declare no conflicts of interest.

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