Original Article

DOI: 10.7860/JCDR/2022/57878.16719

Adverse Drug Reactions to a Daily Fixed-dose Combination Based Antituberculosis Treatment Regime in India's National Tuberculosis Elimination Programme: A Prospective Cohort Study

Internal Medicine Section

KAPIL MATE[1], GYANSHANKAR MISHRA[2], RADHA MUNJE[3]

ABSTRACT

Introduction: In India, the daily weight-based, Fixed Dose Combination (FDC) Antituberculosis Treatment (ATT) regime under the National Tuberculosis Elimination Programme (NTEP) was introduced, replacing the previous intermittent regime with the aim of improving compliance, decreasing Adverse Drug Reactions (ADRs) and thus ultimately translating to improved treatment outcomes. The ADRs are an important factor that can adversely impact the treatment compliance and outcomes of an ATT regime. There is currently a paucity of studies reflecting the development of ADRs in the Indian population to the new ATT regime.

Aim: To study the ADRs of daily FDC-based first-line ATT regime under NTEP.

Materials and Methods: A prospective cohort analysis was conducted in the Department of Respiratory Medicine at Indira Gandhi Government Medical College (tertiary care centre), Nagpur, Maharashtra, India, from January 2019 to September 2020. Total 750 People With Tuberculosis (PWTB) were enrolled in the study. They were administered a standardised daily FDC first-line ATT regime under NTEP comprising of initial two months of intensive phase with Isoniazid (INH or H), Rifampicin (R), Ethambutol (E), and Pyrazinamide (Z) followed by a continuation phase of four months with INH, rifampicin, and ethambutol (2EHRZ/4HRE). Clinical evaluation and/or laboratory investigations were used at baseline and when clinically indicated during therapy to identify treatment-related adverse events.

Results: Among the 750 PWTB, 402 (53.60%) were females, and 348 (46.40%) were males. The mean age of PWTB was 36.46±15.6 years. The ADR to ATT was present in 271 (36.13%) PWTB, 217 (80.07%) were managed on an Outpatient Department (OPD) basis and 54 (19.93%) patients required hospitalisation. Causality assessment revealed that most ADRs were probable (81.18%), followed by possible (18.82%). Regarding the severity of ADRs, 87.08% were mild, 11.44% were moderate, 1.48% were severe, and none of the ADRs was life-threatening. In 67.9% of PWTB, gastrointestinal ADRs were seen, followed by joint pain (37.64%) and cutaneous drug reactions (16.60%). Female PWTB, People Living with Human Immunodeficiency Virus and Tuberculosis (PLHIV-TB), and PWTB with systemic co-morbidities, especially diabetes and systemic hypertension, were at a higher risk of developing ADRs. The risk of ADRs was unaltered with age distribution, body mass index distribution, type of diet, the type of tuberculosis, or the pill burden. Addiction to alcohol and tobacco did not significantly alter the risk of ADRs.

Conclusion: The ADRs caused by daily FDC-based ATT are common, but most are mild and can be managed on an OPD basis. Gastrointestinal ADRs, arthralgia, and cutaneous drug reactions are the most common ADRs of the daily FDC-based ATT regime. Female PWTB, PLHIV-TB, and PWTB with systemic co-morbidities, especially diabetes and systemic hypertension, being at a high risk of developing ADRs, need to be actively screened for ADRs during treatment.

Keywords: Cutaneous drug reactions, Ethambutol, Isoniazid, Pyrazinamide, Rifampicin

INTRODUCTION

Tuberculosis (TB) is an important infectious disease globally. In India, the Revised National Tuberculosis Control Programme (RNTCP) has recently been renamed the National Tuberculosis Elimination Programme (NTEP), reaffirming India's commitment to TB elimination by 2025, five years ahead of global targets [1]. With the implementation of the new and precise daily weight-band-based Fixed Dose Combination (FDC) Antituberculosis Treatment (ATT) regime under NTEP, a relatively accurate anti-TB drug dosing is now possible. This can reduce the occurrence of anti-TB drug Adverse Drug Reactions (ADRs) in the treatment regimen.

The World Health Organisation (WHO) defines ADR as a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [2]. Treatment of TB necessitates the consumption of more than one drug for a prolonged time by the patients. This can lead to the development of various ADRs, which in turn may be dependent on factors like demographic, genetic, nutritional, and co-morbidities in the PWTB [3]. The ADRs to anti-TB medications are a common cause of treatment interruption; therefore, if recognised and addressed early, treatment interruptions can be reduced, and treatment outcomes can be improved [4].

In India, People With Tuberculosis (PWTB) received intermittent ATT under programmatic conditions before the introduction of the current daily ATT regime [5]. The previous regime had inherent factors for drug resistance, due to which it was gradually phased out as per the existing World Health Organisation (WHO) recommendations [6]. Sinha K et al., found that ADRs were present in 69.01% of PWTB receiving intermittent ATT [7]. A recent study by Kiran M and Nagabhushan H from India reported the ADR profile of 74 people with TB (PWTB) on a daily ATT regime; however, the study did not determine the overall prevalence of ADRs among PWTB as the study was not designed for the same [3]. The overall burden of ADRs directly attributable to the currently recommended, new daily weight-based FDC-ATT under NTEP in the Indian population is poorly quantified. There has been a scarcity of research on ADRs to the new ATT regime since the introduction of daily weight-based

FDCs under NTEP. The current study aimed to evaluate the adverse effects of the daily FDC-based ATT regime under the NTEP.

MATERIALS AND METHODS

It was a prospective cohort study conducted in central India between January 2019 and September 2020 in the Department of Respiratory Medicine at Indira Gandhi Government Medical College, Nagpur, Maharashtra, India, a tertiary care referral centre with a NTEP-designated Tuberculosis Unit (TU) and Tuberculosis Diagnostic Centre (TDC). Institutional Ethics Committee, Board of Research Studies of the Institute and State NTEP Operational Research Committee approved the study (Approval letter numbers: 1. IGGMC/Pharm/IEC/263/2018, 2. MUHS/Medical/MUHS-014263/2019 and 3. Jt.DHS/TB&L/Desk-RNTCP/TB/16802-09/19). After written informed consent, eligible people were enrolled in the study.

Inclusion criteria: All the people attending Respiratory Medicine Outpatient Department/Inpatient Department (OPD/IPD) and diagnosed with TB (pulmonary/extrapulmonary), aged more than 13 years, and registered at the study site, Tuberculosis Unit during the study period were included.

Exclusion criteria: People diagnosed with drug-resistant TB, critically ill/morbid patients, PWTB not providing consent for the study, PWTB on rifabutin base ATT (HIV-TB patients on second-line Antiretroviral Therapy (ART) regimen where ATT regimen had been modified), and PWTB with deranged Liver Function Tests/Kidney Function Tests (LFT/KFT) at baseline were excluded from the study.

Study Procedure

Pretreatment investigations

- Sputum smear for Acid Fast Bacilli/Cartridge-Based Nucleic Acid Amplification Test (AFB/CBNAAT).
- For all pulmonary TB patients: chest radiograph.
- HIV testing by enzyme-linked immunosorbent assay (ELISA) method, LFT, KFT, and random blood sugar.

During the study period, any other investigation as clinically required was performed for ADR evaluation.

The standardised weight band-based daily FDC first line ATT regime under NTEP comprised of initial two months of intensive phase with isoniazid (INH), rifampicin, ethambutol, and pyrazinamide followed by a continuation phase of four months with INH, rifampicin, and ethambutol. At baseline and monthly intervals for six months after treatment commencement, patients were evaluated by doctors trained in NTEP standards for clinical evaluation. The occurrence of adverse events was the primary outcome variable. Before treatment initiation and throughout all follow-up visits, all the patients and their family members were counselled about the possibility of adverse events and encouraged to report them. The doctor assessed the PWTB for possible adverse events at each follow-up appointment and recorded the same in the case record forms. Thus, any adverse events, if found, were noted and managed at each visit, depending on clinical and/or laboratory evidence. All ADRs found in the study were reported to the Pharmacovigilance Programme of India (PvPI).

The severity of anti-TB drug-related ADR was classified as follows [8]:

- **Mild:** The ADR did not interfere significantly with the patient's normal functioning.
- **Moderate:** The ADR produced some impairment in the patient's functioning but was not hazardous to the patient's health.
- **Severe:** The ADR produced significant impairment or incapacitation of functioning.
- **Life-threatening:** The ADR caused extreme impairment of functioning, requiring hospitalisation, and if left untreated, could result in the patient's death.

The causality of ADRs was assessed using the Naranjo algorithm scale [9].

STATISTICAL ANALYSIS

A total enumerative sampling technique was used. The data entry was done in the Microsoft Excel spreadsheet. The final analysis was done using Statistical Package for Social Sciences (SPSS) software version 26.0. The presentation of the categorical variables was done in the form of numbers and proportions (%). On the other hand, the continuous variables' presentation was mean±standard deviation (SD) and median (25^{th}-75^{th} percentile) values. The association of quantitative and qualitative variables were analysed using the independent t-test and Chi-square test/Fischer's Exact test, respectively. For statistical significance, the p-value of less than 0.05 was considered significant.

RESULTS

Among 750 PWTB, 402 (53.60%) were females, and 348 (46.40%) were males. The mean age of PWTB was 36.46±15.6 years, with a median of 33 (24-47) years.

Adverse drug reactions to ATT were present in 271 (36.13%) PWTB. More than a third of PWTB on daily FDC-based ATT developed at least one ADR. Distributions of causality and severity of ADRs are shown in [Table/Fig-1]. Of 271 PWTB reporting ADR of anti-TB drugs, 217 (80.07%) PWTB were managed on an OPD basis, and 54 (19.93%) required hospitalisation.

Variables	Frequency	Percentage
Causality score		
Definite ADR	0	0
Probable ADR	220	81.18%
Possible ADR	51	18.82%
Doubtful ADR	0	0
Total	271	100%
Severity of ADR		
Mild	236	87.08%
Moderate	31	11.44%
Severe	4	1.48%
Life threatening	0	0
Total	271	100%

[Table/Fig-1]: Distributions of causality and severity of ADRs among patients developing ADRs to ATT.

The pattern of ADRs among PWTB on ATT is shown in [Table/Fig-2]. The most common ADRs were gastrointestinal disturbances, hepatitis followed by joint pain, and cutaneous drug reactions. [Table/Fig-3] shows the treatment interruption/modification distribution among PWTB with/without ADR.

Various pattern of adverse drug reaction	Frequency	Percentage
Gastrointestinal ADRs (n=184)		
Vomiting	68	25.09%
Abdominal pain	53	19.56%
Hepatitis*	37	13.65%
Asymptomatic elevation of liver enzymes	10	3.69%
Nausea	8	2.95%
Loose motion	8	2.95%
Arthralgia (n=102)	102	37.64%
Cutaneous drug reaction (n=45)		
Itching all over the body	37	13.65%
Skin rash	2	0.74%
Oral ulcer	2	0.74%
Morbilliform rash	1	0.37%
Lichenoid eruption	1	0.37%
Exfoliative dermatitis	1	0.37%
Hair fall	1	0.37%

Peripheral neuropathy (n=3)		
Tingling sensation	2	0.74%
Sensory axonal neuropathy	1	0.37%
Loss of vision	2	0.74%
Vertigo	1	0.37%

[Table/Fig-2]: Pattern of ADRs amongst patients on ATT reporting ADR.

Overall outcome	Frequency	Percentage
Without ADR	479	63.87%
No interruption/modification	479	100%
With ADR	271	36.13%
No interruption/modification	159	58.67%
ADR related self-treatment interruption by patient	95	35.06%
ADR related physician advised treatment interruption/ modification	17	6.27%

[Table/Fig-3]: Analysis of treatment interruption/modification among study subjects.

Of 750 PWTB, the proportion of females was significantly higher among those developing ADR {(160/271) 59.04%} as compared to those without ADR {(242/479) 50.52%} (p-value=0.025). Among 27 people living with HIV-TB (PLHIV-TB), a greater proportion (17/27 (62.96 %)) had ADRs {10/27 (37.04%)} (p-value=0.003). The proportion of diabetes and hypertension was significantly higher in PWTB reporting ADR than those not reporting any ADR. (Diabetes: 8.86% vs 1.25% respectively, p-value <0.0001) and (Systemic hypertension:8.86% vs 1.04% respectively) (p-value <0.0001).

There was no significant association between the occurrence of ADRs and age distribution (p-value=0.268), BMI distribution (p-value=0.668), type of diet (Vegetarian vs mixed pattern of diet) (p-value=0.807), the type of tuberculosis (pulmonary vs extrapulmonary) (p-value=0.051), or the number of FDC tablets as per weight-band (p-value=0.319). Further we could not find any significant association between the occurrence of ADRs and distribution of addiction to alcohol (p-value=0.292), tobacco smoking (p-value=0.068), and smokeless tobacco (p-value=0.952).

DISCUSSION

The current study evaluated the adverse effects of the daily FDC-based ATT regime under the NTEP. It was found that 36.17% of PWTB, who were started on a standardised daily FDC first-line ATT regimen under NTEP, experienced one or more ADRs. The proportion of ADRs to ATT in India and around the world before implementing this regime ranged from 28.61% to 52.9% [Table/Fig-4].

Author	Year	Country	Incidence of ADR
Present study, 2022	2021	India	Among 750 TB patients, 271 (36.13%) patients developed one or more ADR.
Marra F et al., [40]	2007	Canada	Among 1061 TB patients, 318 (30%) patients developed one or more ADR.
Damasceno GS et al., [10]	2013	Brazil	Among 176 TB patients, 73 (41.5%) developed one or more ADR.
Farazi A et al., [21]	2014	Iran	Among 940 TB patients, 269 (28.61%) developed one or more ADR.
Athira B et al., [41]	2015	India	Among 511 TB patients, 93 patients (18.20%) developed adverse drug reactions.
Venkateswarlu K et al., [42]	2017	India	Among 119 TB patients, 63 (52.9%) patients developed one or more ADR.

[Table/Fig-4]: Studies on ADR among TB patients on ATT.

Causality and severity of ADRs: Most ADRs to ATT in this study were of probable or possible category, consistent with previous research [10]. Furthermore, majority of the TB patients had mild ADR. This is reflected in the fact that we managed most ADRs (80.07%) in the outpatient setting, with only 19.93% of PWTB requiring hospitalisation owing to ADR-related issues. This finding suggests that most ADRs can be handled in the outpatient setting or the field, provided healthcare staff are sufficiently trained to recognise and manage them early. It also obviates the requirement for most PWTB with mild ADRs to be referred to tertiary care centres. PWTB must also be reassured right from the commencement of treatment that most ADRs are minor and may be treated symptomatically. This is critical since ADRs to ATT can result in the PWTB being lost to follow-up.

Pattern of ADRs: It was observed that gastrointestinal ADRs, joint pain, and cutaneous drug reactions were the most common ADRs among PWTB initiated on a daily FDC-based ATT regime under the NTEP. [Table/Fig-5] lists the three most common ADRs to ATT observed in various other studies.

Author	Year	Country	The top three ADRs reported in the study
Present study, 2022	2021	India	Among 271 patients who experienced ADRs, the most common ADRs were: 1) Gastrointestinal symptoms in 184 (67.9%) patients, including hepatitis in 30 (11.07%) patients. 2) Joint pain (arthralgia) in 102 (37.64%) patients. 3) Cutaneous drug reactions in 45 (16.60%) patients.
Yee D et al., [20]	2003	Montreal, Canada	1) Rash in 18 (4%) patients. 2) Hepatitis in 12 (3%) patients. 3) Gastrointestinal symptoms in 8 (2%) patients.
Chhetri AK, [19]	2008	Pokhara, Nepal	1) Tingling and burning sensation in hands and feet in 32 (11.03%) patients. 2) Joint pain in 30 (10.34%) patients. 3) Dermatological manifestations (Generalised itching/itchy rashes) in 29 (10%) patients.
Sinha K et al., [7]	2013	Agartala, India	1) Gastrointestinal ADRs in 49 (69.01 %) of 71 TB patients. 2) Generalised weakness in 12 (16.9%) patients. 3) Liver dysfunction in 11 (15.49%) patients.
Mandal PK et al., [5]	2013	Kolkata, India	1) Gastrointestinal symptoms in 6 (15%) patients. 2) Clinical Jaundice in 3 (7.5%) patients. 3) Itching, rash in 2 (5%) and arthralgia 2 (5%) patients, respectively.
Farazi A et al., [21]	2014	Arak, Iran	1) Liver dysfunction in 39 (19.4%) patients. 2) Allergic reaction in 23 (26.7) patients. 3) Gastrointestinal disorders in 10 (8.1%) patients.
Xi Qin Han et al., [32]	2017	China	1) Hyperuricemia in 230 (65.0%) patients. 2) Hepatotoxicity in 22 (6.2%) patients. 3) Hearing disturbances in 17 (4.8%) patients.
Fei CM et al., [28]	2018	Pulau Pinang, Malaysia	1) Cutaneous adverse drug reactions (21.0%). 2) Drug-induced hepatitis (7.1%). 3) Gastrointestinal disturbance (4.8%).

[Table/Fig-5]: The patterns of adverse drug reactions to anti TB drugs (Top 3 ADRs reported) in various studies.

Gastrointestinal: In this study, gastrointestinal symptoms were one of the most common ADRs among PWTB reporting ADRs, accounting for 67.9% of cases. Sinha K et al., found gastrointestinal ADRs as the most common ADRs to ATT, similar to the present findings [7]. Any anti-TB medication administered orally has the risk of causing drug-induced gastritis. The NTEP guidelines recommend specific non pharmacological measures before initiation of pharmacotherapy for gastrointestinal ADRs like nausea and vomiting. These include reassuring the patients and asking them to take the pills with less water and over a longer duration (20 minutes). Eating the pills embedded in a banana also helps. Once the non pharmacological interventions do not yield the desired symptomatic relief, then pharmacological management with antiemetics (e.g., domperidone) and proton pump inhibitors (e.g., omeprazole) or H2-blocker (e.g., ranitidine) may be initiated [11].

It was found in the present study that 13.65% of PWTB with ADRs had ATT-induced hepatitis, and 3.69% had asymptomatic elevations in liver enzymes. Like the present study, Gulbay BE et al., found an asymptomatic increase in liver enzymes in 4.9% of PWTB. A brief asymptomatic rise in transaminase or acute liver failure can

be signs of ATT-induced hepatotoxicity [12]. The three primary anti-TB medications, isoniazid, rifampicin, and pyrazinamide, can cause liver toxicity [13]. An increase in serum Aspartate Aminotransferase (AST) and/or serum Alkaline Transaminase (ALT) of more than three times the upper limit of normal in the presence of symptoms such as nausea, vomiting, anorexia, or pain in the abdomen, or the presence of transaminases of more than five times the upper limit of normal without symptoms, and/or raised total bilirubin, is considered "hepatotoxicity" while receiving ATT [14]. In the Indian population, ATT-induced hepatotoxicity has been observed to be 11.5%. However, a meta-analysis indicated that the risk is 4-28% in the west [15,16]. Hepatotoxicity causes significant morbidity and mortality. The treatment regimen may need to be changed at times and replaced with a relatively "hepatosafe" ATT regime (consisting of aminoglycoside, fluoroquinolone, and ethambutol) until the resolution of ATT-induced hepatitis [14]. As a result, early identification of PWTB at risk of hepatotoxicity is critical. In this regard, one of the important clinical recommendations by the NTEP guidelines is that if a PWTB is found to be alcoholic, the patient should be advised to refrain from alcohol strictly. Alcohol consumption increases the chances of the patient developing hepatitis, irregularity in drug intake, and adverse treatment outcomes [11].

Arthralgia: It was observed that 37.63% of PWTB with ADRs suffered from joint pain. Pyrazinamide and ethambutol, two antituberculous medicines, have been observed to cause hyperuricemia and arthralgia in non-gouty patients. The process is connected to pyrazinoic acid, the primary metabolite of pyrazinamide that is oxidised by xanthine oxidase and suppresses uric acid secretion in the renal tubules [17]. Ethambutol, through renal uric acid clearance lowering, can produce hyperuricemia in rare cases [12]. When used with ethambutol, pyrazinamide has an additive effect on increasing the proportion of drug-induced hyperuricemia [17]. INH can occasionally cause non hyperuricemic arthritis [18]. The management is mainly symptomatic with Non Steroidal Anti-inflammatory Drugs (NSAID). However, uric acid lowering drugs (e.g., colchicine, febuxostat) must be administered in addition to NSAIDs to manage hyperuricemic arthritis [11]. Serum Uric acid estimation should therefore always be done in PWTB on ATT, who complain of joint pains.

Cutaneous: It was observed that 16.61% of PWTB reporting ADRs had cutaneous drug reactions to anti-TB medicines. Cutaneous drug reactions were noted by Sinha K et al., in 8.45% of PWTB and Chhetri AK et al., in 33.33% of PWTB reporting ADRs to ATT [7,19]. Most cutaneous drug reactions, such as itching or a localised rash, respond to antihistaminic therapy. Cutaneous drug reactions involving more than 10% of body surface area or mucus membrane involvement require stopping ATT. After the skin lesions have subsided, ATT can be restarted with an ATT drug challenge, wherein individual drugs are introduced one at a time in incremental doses [11].

Peripheral neuropathy: It was observed that 1.11% of PWTB with ADRs had peripheral neuropathy. Mandal K et al., also noted peripheral neuropathy in 2.5% of PWTB reporting ADR to daily FDC-based ATT regime [5]. INH is the most commonly suspected drug responsible for peripheral neuropathy, while it has also been linked with ethambutol [19]. INH-induced peripheral neuropathy is treated with pyridoxine. At present, NTEP recommends administrating pyridoxin prophylaxis to patients on the ATT FDC regime for drug-sensitive TB (2EHRZ/4HRE), who are at a high risk of developing peripheral neuropathy, i.e., patients with malnutrition, chronic alcohol dependence, PLHIV, renal failure, diabetes, pregnant women, or breastfeeding mothers. Under NTEP, the recommended prophylactic dose of pyridoxine is 10 mg/day in children, 25 mg/day in adults, and 50 mg/day in adult PLHIV [11].

Ophthalmic ADRs: The current study found the ophthalmic ADRs associated with ATT in 0.27% of PWTB. According to Yee D et al., visual toxicity was detected in 0.2% of PWTB on ATT, while Farazi A et al., noted a loss in eyesight in 0.5% of PWTB on ATT [20,21]. Thus, ethambutol-induced optic neuritis is a rare but serious ADR. It is usually reversible and proportional to the dose and duration of the treatment received, but it can infrequently become irreversible, resulting in persistent visual impairment, particularly in the elderly [22]. Ethambutol-associated retrobulbar neuritis may manifest as visual field constriction, central and peripheral scotomas, and green-red colour blindness [23]. However, blue-yellow (Tritan) colour defects are the most common, usually occurring earlier, while red-green (Protan) colour defects occur later [24]. This necessitates screening for colour vision defects, including blue-yellow defects, which are missed by the commonly used colour vision charts like the Ishihara chart and require other specific charts/tests like the F-M100 hue test. As ethambutol is now included in the NTEP's intensive and continuation phases of ATT, we must be aware and highly vigilant in the early detection of its ocular ADRs. The presence of ATT-associated ophthalmic ADR usually requires withdrawal of ethambutol.

Giddiness: One study subject developed giddiness as an ADR of the anti-TB drugs. Pyrazinamide may rarely cause giddiness [25].

Risk factors for the development of ADRs: Among PWTB, it was observed that females, PLHIV-TB, and those with systemic co-morbidities, especially diabetes and systemic hypertension, were at a higher risk of developing ADRs.

Similar to the present study, other studies have also found a female preponderance in the ADRs to ATT [19,26-28]. This might result from the pharmacokinetic, immunological, and hormonal variations between the genders. Compared to males, females often have lower lean body mass, lesser hepatic clearance, altered Cytochrome P450 (CYP) enzyme activity, and different rates of drug metabolism. Conjugation, absorption, protein binding, and renal excretion are other crucial aspects that could alter depending on gender. ADRs such as cutaneous drug responses in females may be explained by gender differences in T-cell activation and proliferation [19,29]. Also, women seeking healthcare may face cultural and socioeconomic challenges, resulting in a delayed presentation and more severe illness, which may contribute to ADR development [30]. As a result, among PWTB, females may be at a higher risk of developing ADRs than males [31].

People with diabetes were at a higher risk of ADRs due to ATT in our study, a finding congruent with the existing literature [32]. A robust bidirectional screening, i.e., screening people with diabetes for TB and vice-versa is imperative [33]. Chronic hyperglycaemia, a complication of diabetes, causes long-term damage, dysfunction, and failure of various organs, including the kidneys, nerves, and eyes. Renal impairment can reduce the metabolism of anti-TB medications [34].

It was observed that PLHIV had a higher incidence of ADRs of ATT, consistent with previous research [35,36]. Studies have found that PLHIV-TB are more likely to experience major ATT adverse event [37]. This is due to a combination of drug toxicity, drug-drug interactions, regimen complexity, and a high pill burden [35]. ADRs are a major challenge in both tuberculosis and HIV national programmes. ADR may adversely affect treatment compliance, leading to therapeutic failure and potentially contributing to MDR-TB.

Thus, during the ATT course, PLHIV, diabetics, and/or hypertensives must be regularly monitored for ADRs and have their co-morbidities managed well.

Even though the present study population's addiction profile (alcohol intake, tobacco use, and smokeless tobacco use) did not suggest that PWTB with varied addiction habits were at a high risk of developing ADRs to anti-TB medications, addiction habits can adversely affect TB patients' treatment outcomes. As a result, patients should be prevented from engaging in addictive behaviours from the beginning of therapy, and deaddiction strategies can be

used as a part of the standard pretreatment assessment of such patients [11].

Treatment interruption/modification: ADR-related treatment discontinuation or modification was seen in 41.32% of PWTB in the current study. Because ADRs can cause treatment interruption in many PWTB, early detection and management of ADRs are critical for improved treatment outcomes. According to the present study, a sizable proportion of patients (35.06 %) had self-interrupted anti-TB medication due to ADRs before reporting to the healthcare facility for clinical evaluation and management of ADRs. Patient's self-interruptions of anti-TB medications due to ADRs must be reduced. ADRs of ATT can be a major reason for being lost to follow-up and can thus adversely affect treatment outcomes [4]. As a result, ADRs in patients on ATT must be closely monitored, diagnosed early, and managed accordingly.

Today, both the public and private sectors are contributing significantly to TB healthcare in India [38]. TB treatment regime in the public sector has improved considerably over time, filling the lacunae in previous treatment standards [6,39]. Proper and timely diagnosis and management of ADRs will further increase treatment compliance and improve treatment outcomes.

Recording and reporting ADRs should be an ongoing and dynamic process that improves our monitoring and treatment strategies. Such facilities available under the Pharmacovigilance Programme of India (PvPI) should be utilised to the fullest.

In the NTEP field conditions, this result has a great clinical utility. TB management requires a thorough pretreatment evaluation, counselling, and aggressive screening for adverse events during routine follow-ups. Under programmatic conditions, the findings of the present study can be used in targeted management programme/modules of ADR management. Such training programme must focus on identifying and managing common ADRs like gastrointestinal ADRs (gastritis, hepatitis), joint pains, and cutaneous drug reactions.

To the best of authors knowledge, the current study on a cohort of 750 PWTB following the introduction of the new daily FDC-based ATT regime is the largest in India to study the ADRs of ATT under programmatic conditions. The current research was prospective, with a six month follow-up period. Thus, any ADRs occurring during the treatment period were actively recorded and reported. Authors evaluated co-morbidities and could determine some crucial determinants of ADR of anti-TB drugs. The ADR's causality and severity were adequately assessed and reported. The proportion of ADRs to ATT in India and around the world before implementing this regime ranged from 28.61% to 52.9% [40-42].

Limitation(s)

Adverse drug reactions beyond six months of ATT duration were not captured in the study. Some mild ADRs might have gone unnoticed because of poor recollection of the enrolled study participants. PWTB under 13 years of age were excluded. Being a single-centre study with a relatively homogeneous sample, the results cannot be generalised. It was challenging to identify the individual causative drugs for ADRs of FDC ATT regime in all cases because many of the frequent ADRs, such as drug-induced gastritis and hepatitis, overlapped.

CONCLUSION(S)

More than a third of PWTB receiving FDC-based ATT experienced ADR, most of which were minor and treated in the outpatient setting. Gastrointestinal ADRs, arthralgia, and cutaneous drug reactions are the most common ADRs of the daily FDC-based ATT regime. Female PWTB, PLHIV-TB, and PWTB with systemic co-morbidities, especially diabetes and systemic hypertension, being at a high risk of developing ADRs, need to be actively screened for ADRs during treatment.

Acknowledgement

The authors are thankful to the faculties: Dr. Sanjay Gour, Dr. Dhiraj Bhatkar, Dr. Jitesh Atram, and resident doctors: Dr. Ninu, Dr. Pradip, Dr. Rahul, Dr. Madhav, Dr. Govinda, Dr. Amol, Dr. Virendra, Dr. Divya, Dr. Asha, Dr. Ashish, Dr. Dhaval, Dr. Dinesh, Dr. Neha, Dr. Anjali, Dr. Kriti, Dr. Anish, and Dr. Dattatraya, from the Department of Respiratory Medicine, IGGMC Nagpur for their active help in the evaluation and clinical management of the cases. The authors would also like to thank Dr. Sadaf Khateeb, MO-NTEP, at the IGGMC TU, for her assistance with patient enrolment and reporting ADRs to the PvPI. The authors express gratitude to the NTEP for funding the research study. NTEP provided funding for the research study through a thesis grant after approval by the Maharashtra state NTEP Operational Research Committee. The authors have no conflicts of interest to declare.

REFERENCES

[1] NTEP- renamed in 2020- TBFacts. [cited 2021 Mar 13]. Available from: https://tbfacts.org/ntep/.
[2] World Health Organisation (WHO). Requirements for Adverse Reaction Reporting. Geneva, Switzerland: World Health Organisation; 1975.
[3] Kiran M, Nagabushan H. Adverse drug reactions monitoring in patients on antitubercular treatment in tertiary care hospital, Mandya. Biomed Pharmacol J. 2021;14(2):701-08. Available from: https://biomedpharmajournal.org/vol14no2/adverse-drug-reactions-monitoring-in-patients-on-antitubercular-treatment-in-tertiary-care-hospital-mandya/.
[4] Mishra GP, Gandhi SA. Study of various causes of treatment interruption among tuberculosis patients. Indian Journal of Basic and Applied Medical Research. 2016;6(1):382-86. Available from: https://ijbamr.com/pdf/December 2016 382-386 RR.pdf.
[5] Mandal PK, Mandal A, Bhattacharyya SK. Comparing the daily versus the intermittent regimens of the anti-tubercular chemotherapy in the initial intensive phase in non-hiv, sputum positive, pulmonary tuberculosis patients. J Clin Diagn Res. 2013;7(2):292-95. Available from: https://www.jcdr.net/article_fulltext.asp?issn=0973-709x&year=2013&month=February&volume=7&issue=2&page=292&id=2750.
[6] Mishra G, Ghorpade SV, Mulani J. XDR-TB: An outcome of programmatic management of TB in India. Indian J Med Ethics. 2014;(1):47-52. Available from: http://ijme.in/articles/xdr-tb-an-outcome-of-programmatic-management-of-tb-in-india/?galley=html.
[7] Sinha K, Marak IT, Singh Wa. Adverse drug reactions in tuberculosis patients due to directly observed treatment strategy therapy: Experience at an outpatient clinic of a teaching hospital in the city of Imphal, Manipur, India. J Assoc Chest Physicians. 2013;1:50-53. Available from: https://www.jacpjournal.org/article.asp?issn=2320-8775;year=2013;volume=1;issue=2;spage=50;epage=53;aulast=Sinha.
[8] Central Tuberculosis Division. Ready reckoner for medical officers: Adverse drug reactions associated with ready reckoner for medical officers, identification & management anti-tubercular drugs . 2020. Available from: https://drive.google.com/file/d/1otkjE1G4yOIlhAFKu4SPNWficnOhfni_/view.
[9] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. Available from: https://pubmed.ncbi.nlm.nih.gov/7249508/.
[10] Damasceno GS, Guaraldo L, Engstrom EM, Theme Filha MM, Souza-Santos R, Godoi Vasconcelos AG, et al. Adverse reactions to antituberculosis drugs in Manguinhos, Rio de Janeiro, Brazil. Clinics. 2013:68(3):329-37. Available from: https://www.sciencedirect.com/science/article/pii/S1807593222020701?via%3Dihub.
[11] Central TB Division (Ministry of Health and Family Welfare). Training Modules for Programme Managers and Medical Officers (Modules 1-4). 2020;01-283. Available from: https://tbcindia.gov.in/WriteReadData/NTEPTrainingModules1to4.pdf.
[12] Gülbay BE, Gürkan ÖU, Yildiz ÖA, Önen ZP, Erkekol FÖ, Baççioğlu A, et al. Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respiratory Medicine. 2006;100(10):1834-42. Available from: https://www.resmedjournal.com/article/S0954-6111(06)00045-X/fulltext.
[13] Javadi MR, Shalviri G, Gholami K, Salamzadeh J, Maghooli G, Mirsaeedi SM. Adverse reactions of anti-tuberculosis drugs in hospitalized patients: Incidence, severity and risk factors. Pharmacoepidemiology and Drug Safety. 2007;16(10):1104-10.
[14] Singh A, Prasad R, Balasubramanian V, Gupta N, Gupta P. Prevalence of adverse drug reaction with first-line drugs among patients treated for pulmonary tuberculosis. Clinical Epidemiology and Global Health. 2015;3(supplement 1):580-90. Available from: https://www.sciencedirect.com/science/article/abs/pii/S2213398415000731.
[15] Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American thoracic society/centers for disease control and prevention/infectious diseases society of America: Treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603-62. Available from: https://www.atsjournals.org/doi/10.1164/rccm.167.4.603?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.
[16] Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: A meta-analysis. Chest. 1991;99(2):465-71.

[17] Pillai AP, Maldhure BR. Zodpey SP. Hyperuricemia during anti-tuberculous treatment. Lung India. 1999;17(1):19-22.
[18] Periman P, Venkataramani TK. Acute arthritis induced by isoniazid. Annals of Internal Medicine. 1975;83(5):667-68.
[19] Chhetri AK, Saha A, Verma SC, Palaian S, Mishra P, Shankar PR. A study of adverse drug reactions caused by first line anti-tubercular drugs used in Directly Observed Treatment, Short course (DOTS) therapy in western Nepal, Pokhara. J Pak Med Assoc. 2008;58(10):531-36. Available from: https://jpma.org.pk/article-details/1507?article_id=1507.
[20] Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. Am J Respir Crit Care Med. 2003;167(11):1472-77. Available from: https://www.atsjournals.org/doi/10.1164/rccm.200206-626OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.
[21] Farazi A, Sofian M, Jabbariasl M, Keshavarz S. Adverse reactions to antituberculosis drugs in iranian tuberculosis patients. Tuberc Res Treat. 2014;2014:412893. Available from: https://www.hindawi.com/journals/trt/2014/412893/.
[22] Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther. 1997;13(5):473-77.
[23] Imam F, Sharma M, Khayyam KU, Al-Harbi NO, Rashid MK, Ali MD, et al. Adverse drug reaction prevalence and mechanisms of action of first-line anti-tubercular drugs. Saudi Pharm J. 2020;28(3):316-24. Available from: https://www.sciencedirect.com/science/article/pii/S1319016420300190?via%3Dihub.
[24] Makunyane P, Mathebula S. Update on ocular toxicity of ethambutol. Afr Vision Eye Health. 2016;75(1):a353. Available from: https://avehjournal.org/index.php/aveh/article/view/353/586.
[25] Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare Services G of I. Guidelines on programmatic management of drug resistant tuberculosis in India 2021. New Delhi. 2021;1-195. Available from: https://tbcindia.gov.in/showfile.php?lid=3590.
[26] Dhingra VK, Rajpal S, Aggarwal N, Aggarwal JK, Shadab K, Jain SK. Adverse drug reactions observed during DOTS. Journal of Communicable Diseases. 2004;36(4):251-59.
[27] Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: Observations in routine treatment. Tubercle and Lung Disease. 1996;77(1):37-42.
[28] Fei CM, Zainal H, Hyder Ali IA. Evaluation of adverse reactions induced by anti-tuberculosis drugs in hospital Pulau Pinang. Malays J Med Sci. 2018;25(5):103-14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419878/.
[29] Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol. 2001;2(6):349-51. Available from: https://pubmed.ncbi.nlm.nih.gov/11770389/.
[30] Connolly M, Nunn P. Women and tuberculosis. World Health Stat Q. 1996;49(2):115-19. Available from: https://pubmed.ncbi.nlm.nih.gov/9050189/.
[31] Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother. 2004;38(6):1074-79.
[32] Han XQ, Pang Y, Ma Y, Liu YH, Guo R, Shu W, et al. Prevalence and risk factors associated with adverse drug reactions among previously treated tuberculosis patients in China. Biomedical and Environmental Sciences. 2017;30(2):139-42. Available from: https://www.besjournal.com/en/article/doi/10.3967/bes2017.018.
[33] Mishra G, Munje R, Dawkore M. Diabetes and tuberculosis-tackling double trouble. Indian Journal of Basic and Applied Medical Research. 2018;8(1):256-60. Available from: https://www.ijbamr.com/assets/images/issues/pdf/December 2018 256 - 260.pdf.pdf.
[34] Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: Convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46.
[35] Sadiq S, Khajuria V, Tandon VR, Mahajan A, Singh JB. Adverse drug reaction profile in patients on anti-tubercular treatment alone and in combination with highly active antiretroviral therapy. J Clin Diagn Res. 2015;9(10):FC01-04.
[36] Dean GL, Edwards SG, Ives NJ, Matthews G, Fox EF, Navaratne L, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS. 2002;16(1):75-83.
[37] Michael OS, Sogaolu OM, Fehintola FA, Ige OM, Falade CO. Adverse events to first line anti-tuberculosis drugs in patients co-infected with HIV and tuberculosis. Ann Ib Postgrad Med. 2016;14(1):21-29.
[38] Mishra GP. Public-private mix in tuberculosis. Lancet Infect Dis. 2012;12(12):908-09. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(12)70257-8/fulltext.
[39] Mishra G, Mulani J. Tuberculosis prescription practices in private and public sector in India. National Journal of Integrated Research in Medicine. 2013;4(2):71-78. Available from: http://nicpd.ac.in/ojs-/index.php/njirm/article/view/2153/1966.
[40] Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, et al. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. Int J Tuberc Lung Dis. 2007;11(8):868-75.
[41] Athira B, Manju CS, Jyothi E. A study on adverse drug reactions to first line antitubercular drugs in DOTS therapy. International Journal of Pharmacology and Clinical Science. 2015;4(1):07-11.
[42] Venkateswarlu K, Tiwari K, Mamatha E, Vivek S, Shravan P. Study of adverse drug reactions in tuberculosis patients. Journal of Pharma Research. 2017;6(Supple 2):61-65. Available from: https://jprinfo.com/storage/live/2020-04-06%2017_07_0713.K.Venkateswarlu.pdf.

PARTICULARS OF CONTRIBUTORS:
1. Resident Doctor, Department of Respiratory Medicine, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
2. Associate Professor, Department of Respiratory Medicine, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
3. Professor and Head, Department of Respiratory Medicine, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Gyanshankar Mishra,
Associate Professor, Department of Respiratory Medicine, Indira Gandhi Government Medical College, CA Road, Nagpur-440018, Maharashtra, India.
E-mail: gpmishra81@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 28, 2022
- Manual Googling: Jul 22, 2022
- iThenticate Software: Jul 25, 2022 (7%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **May 19, 2022**
Date of Peer Review: **Jul 04, 2022**
Date of Acceptance: **Jul 26, 2022**
Date of Publishing: **Aug 01, 2022**