

## Original Research Article

# Adverse drug reactions among new sputum positive pulmonary tuberculosis patients on daily treatment regimen: a prospective study from Haryana, India

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## ABSTRACT

**Background:** Daily regimen anti-tuberculosis treatment was adopted by Revised National Tuberculosis Control Programme (RNTCP) as a step to achieve tuberculosis elimination by 2025 in India. The change was implemented prior to completion of pilot study, which necessitated this study to note the self-reported Adverse Drug Reactions (ADRs).

**Methods:** A prospective study with concurrent sampling design was carried on from June 2018 to June 2020 in the state of Haryana, India. Pre-tested semi-structured schedule was used to collect data based on RNTCP outcome definitions through two monthly (four visits) home visits. Mean±standard deviation, percentage, proportion and chi-square test was used. The p-value of <0.05 was considered as statistically significant.

**Results:** Amongst 122 study participants 74 (60.7%) were males and 48 (39.3%) were females with mean age of 39.4±18.9 years. Majority were urban residents 87 (71.3%) and 35 (28.7%) rural residents. There were 25 (20.5%) tobacco smokers, nine (7.4%) alcohol consumers, and three (2.5%) smokeless tobacco users. Forty-five participants had ADRs and 54 ADR events had occurred, but none required change in treatment regimen. Sixteen (13.1%) reported loss of appetite followed by 10 (8.2%), flu-like symptoms, eight (6.6%) nausea, seven (5.7%) pain in joints, three (2.5%) abdomen pain, three (2.5%) headache, two (1.6%) itching and rash, one (0.8%) burning in hands and feet and one (0.8%) giddiness. Daily regimen ADR cases (36.9%) and events (44.3%) when comparatively higher than intermittent regimen (25.6%).

**Conclusions:** The ADRs cases and events had occurred in higher proportion but were mild and hence did not require any regimen change.

**Keywords:** Adverse drug reactions, Anti-tuberculosis treatment, Daily regimen, New sputum positive, Pulmonary

## INTRODUCTION

The extent of tuberculosis (TB) in most of the developing countries led to declaration of TB as a global disease by World Health Organization (WHO).<sup>1</sup> It claims to be the ninth leading cause of death worldwide.<sup>2</sup> Various strategies and techniques were used to counter TB. In the

early 1900s TB patients were treated in open-air sanatoriums. Later on, with the advent of new anti-tuberculosis drugs from 1940s led to label TB as a curable disease.<sup>3</sup> In the beginning single drug was used for a varying duration of time to treat TB which increased the chances of treatment failure and relapse cases.<sup>4</sup> So as to provide adequate Anti-Tuberculosis Treatment (ATT)

a combination of multiple drugs was recommended by WHO for a 6 months duration. India had adopted the intermittent drug regimen under RNTCP to treat TB later adopted with Directly Observed Treatment Short-course (DOTS) strategy. The first line drugs isoniazid, rifampicin, pyrazinamide and ethambutol were used.<sup>5</sup> The important aspects of the treatment are the effectiveness of the drug and the extent at which adverse drug reactions can occur. The TB treatment outcomes was seen to be improving since 1994 and achieved a success rate of 85% in 2001.<sup>6</sup> The mortality rate had also been decreasing at 4% per year since 1995.<sup>7</sup> There was a decline of the incidence of tuberculosis cases by 5.6% per year since 1999. The treatment success rate in turn probably decreased the disease duration.<sup>8</sup> During the same time the prevalence of TB drug resistance (DR) in new sputum positive pulmonary TB cases was increasing from 1% to 3%.<sup>9</sup> Primary drug resistance of 4.3% and secondary drug resistance of 15.8% were observed in a study. According to WHO data 2011 and TB India 2013, MDR cases among notified PTB cases ranged from 3.6 to 6.2% that comprises newly diagnosed cases in the range of 1.5-2.7% and retreatment cases up to 17%.<sup>10</sup> This was causing a decrease in the treatment success rates of the MDR and XDR-TB patients to 48% and 30% respectively in 2018.<sup>2</sup> The consequence of an increased chance of treatment failure leading to relapse or resistance or death of the tuberculosis patients steered the government to change its treatment strategy. Vowing to which Government of India (GoI) attempted to conduct a pilot study in 2014 but, a three year delay was witnessed. Hence, in February 2017, Supreme court of India directed to adopt a new strategy of daily regimen treatment to treat tuberculosis patients after a period of nine months without the conclusive report from the pilot study with the aim to eliminate TB by 2025.<sup>11</sup> Every new regimen strategy used for treatment of tuberculosis play a major role in terms of treatment success through compliance which in turn depends on the acceptability to the new drug regimen pertaining to the adverse drug reactions (ADRs). A study reported a varying degree of ADRs from 4.87% to 41.59% was observed among the first line drugs.<sup>12</sup> Thus, the increased dose frequency in daily regimen needs a close observation for ADRs during the treatment course. Not many studies are available in India on the ADRs of daily regimen ATT. Hence, this study was conducted to assess the occurrence of ADRs during the study period.

## METHODS

Prospective study with concurrent sampling design was done in Tuberculosis units (TU) in Sonipat District, Haryana. New sputum positive pulmonary tuberculosis cases registered under NIKSHAY portal in Sonipat District were taken as a study sample.

Among the seven TUs in Sonipat District, Sonipat TU was selected randomly by lottery method and all new sputum positive pulmonary tuberculosis cases registered in NIKSHAY portal under RNTCP of the immediate

quarter i.e., second quarter from 1st April 2019 to 30th June 2019 were enrolled concurrently on weekly basis. Inclusion and exclusion criteria was applied to this universal sample to obtain the study participants. The participants were contacted telephonically to obtain their detailed address and appointment for home visit to collect data using a pre-tested semi-structured schedule was made. They were followed up at a two monthly interval for six months i.e., total four contacts were made.

## Study variables

Age, gender, area of residence, consumption of alcohol, tobacco use and self-reported adverse drug reactions based on standard document of Central Tuberculosis Division, Government of India on 'prevention and management of adverse reactions associated with anti-tuberculosis drugs 2016' were noted during the four visits from the initiation of the treatment to completion of continuation phase with a two monthly interval.<sup>13</sup>

## Inclusion criteria

All new sputum positive pulmonary tuberculosis patients who were residents of Sonipat district and those who gave the informed consent were included in the study.

## Exclusion criteria

All patients with co-morbid HIV and diabetes, and patients transferred in or transferred out were excluded.

## Data collection

All the new sputum positive pulmonary tuberculosis patients registered under NIKSHAY portal were enrolled concurrently on weekly basis. The patients were contacted telephonically to obtain their detailed address and appointment to visit them at their home to collect data using a pre-tested semi-structured schedule. The patients were followed up at an interval of two months till the end of their treatment i.e., total four contacts were made. From the first contact (within fortnight of enrolment) socio-demography data; age, gender, area of residence, personal habits like alcohol consumption and tobacco use were noted. During the further contacts that is, second contact at the end of intensive phase (after 2 months of treatment initiation), third contact at the mid of continuation phase (after 4 months of treatment initiation) and fourth contact at treatment completion (after 6 months of treatment initiation) the self-reported adverse drug reactions were noted.

## Statistical methods

Mean±standard deviation was calculated for quantitative data, percentage and proportion were calculated for qualitative data. Chi-square test was used to find out the association between dependent and independent

variables. The p-value of <0.05 was considered as statistically significant.

### Ethical considerations

Study was approved by the Institutional Ethics Committee Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan Sonipat. Permission from the Civil Surgeon of District Sonipat was obtained to conduct the study. The anonymity and confidentiality of the data of study participants was ensured by coding the participants.

## RESULTS

The tuberculosis patients registered under NIKSHAY portal during the second quarter of the year 2019 were 360 patients. Out of which 122 study participants had met the inclusion criteria. Amongst those patients the majority were males 74 (60.7%) and remaining 48 (39.3%) were females. None of the other gender were reported to be new sputum positive pulmonary tuberculosis patients in this study population. The youngest study participant was six years and the eldest of 83 years of age. The mean age of study participants was  $39.4 \pm 18.9$  years, median age was 35 years and the mode was 30 years. Majority of them were urban area residents that is 87 (71.3%) and remaining 35 (28.7%) rural areas (Table 1). Based on the distribution of study participants according to their personal habits in Table 2, a greater number were tobacco

smokers that is 25 (20.5%), followed by nine (7.4%) alcohol consumers, and three (2.5%) smokeless tobacco users.

**Table 1: Socio-demographic profile of the study participants.**

Variables	N (%) (n=122)
<b>Gender</b>	Male 74 (60.7)
	Female 48 (39.3)
	Others 0 (0.0)
<b>Age in completed years</b>	06-25 36 (29.5)
	26-45 41 (33.6)
	46-65 33 (27.1)
	66-85 12 (9.8)
<b>Area of residence</b>	Rural 35 (28.7)
	Urban 87 (71.3)

**Table 2: Distribution of the study participants according to their personal habits.**

Habits	Male n=74 (%)	Female n=48 (%)	Total n=122 (%)
<b>Tobacco</b>	Smoke 24 (32.4)	1 (2.1)	25 (20.5)
	Smokeless 1 (1.4)	2 (4.2)	3 (2.5)
<b>Alcohol</b>	9 (12.2)	0 (0.0)	9 (7.4)
<b>Drug abuse</b>	0 (0.0)	0 (0.0)	0 (0.0)

Note: Some participants had multiple habits

**Table 3: Distribution of the study participants based on their self-reported adverse drug reactions during the study period.**

Profile of adverse drug reactions	During 1 <sup>st</sup> contact n=122 N (%)	During 2 <sup>nd</sup> contact n=115 N (%)	During 3 <sup>rd</sup> contact n=113 N (%)	During 4 <sup>th</sup> contact n=113 N (%)	Total n=122 N (%)
<b>Nausea</b>	3 (2.5)	8 (6.9)	1 (0.9)	0 (0.0)	8 (6.6)
<b>Vomiting</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Loss of appetite</b>	17 (13.9)	15 (13.0)	3 (2.7)	2 (1.7)	16 (13.1)
<b>Pain in abdomen</b>	1 (0.8)	2 (1.7)	2 (1.8)	1 (0.9)	3 (2.5)
<b>Yellow skin/eyes/dark colored urine</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Tingling/burning/numbness in hands and feet</b>	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.8)
<b>Flu like symptoms</b>	0 (0.0)	9 (7.8)	1 (0.9)	1 (0.9)	10 (8.2)
<b>Itching and rash</b>	0 (0.0)	2 (1.7)	1 (0.9)	1 (0.9)	2 (1.6)
<b>Reduced vision/any eye problem</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Pain in joints</b>	5 (4.1)	7 (6.1)	3 (2.7)	3 (2.7)	7 (5.7)
<b>Reduced/loss of hearing</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Tinnitus</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Giddiness/loss of balance</b>	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.8)
<b>Swelling of face/neck</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Disproportionate weight gain</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Pale look/ headache/palpitations</b>	0 (0.0)	4 (3.5)	0 (0.0)	0 (0.0)	3 (2.5)
<b>Convulsions</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Others</b>	0 (0.0)	3 (2.6)	2 (1.8)	1 (0.9)	3 (2.5)
<b>Total no of participants reporting one or more symptoms</b>	20 (16.4)	43 (37.4)	12 (10.6)	9 (8.0)	45 (36.9)

Note: There are different number of participants because some of them died, transferred out or lost to follow-up. For some participants the symptoms extended over more than one contact duration.

**Table 4: Comparison of the adverse drug reactions occurrence in intermittent regimen and daily regimen ATT for new sputum positive pulmonary tuberculosis.**

	Intermittent regimen of ATT (Previous study) <sup>24</sup> n=43	Daily regimen of ATT (Present study) n=122	P-value
<b>ADR cases</b>	25.6%	36.9%	0.178
<b>ADR events</b>	25.6%	44.3%	0.031

Among males 24 (32.4%) were tobacco smokers, followed by nine (12.2%) alcohol consumers and one (1.4%) smokeless tobacco user. Whereas in females two (4.2%) were smokeless tobacco users and one (2.1%) was tobacco smoker.

The self-reported ADRs of the study participants during the study period (table 3) out of 122 participants only 45 (36.9%) participants had reported different ADRs during different phases of the study. A total of 54 ADR events were reported. Sixteen (13.1%) of study participants reported experiencing loss of appetite followed by 10 (8.2%) flu-like symptoms, eight (6.6%) nausea, seven (5.7%) pain in joints, three (2.5%) pain in abdomen, three (2.5%) headache, two (1.6%) itching and rash, one (0.8%) burning in hands and feet and one (0.8%) giddiness. There were three (2.5%) of study participant who had reported symptoms that were not listed under prevention and management of adverse participant had reported constipation, one (0.8%) with persistent cough and one (0.8%) with chest pain. At first the frequency occurrence of ADRs increased from 16.4% to 37.4% during the first and second contact respectively. Later decreased to 10.6% and 8.0% during the third and fourth contact.

Our study was conducted among new sputum positive pulmonary tuberculosis patients on daily regimen of ATT under RNTCP. The participants were followed up through face to face interviews at regular intervals for six months from the start of the treatment till an outcome had occurred. Adverse drug reactions were observed as one of the outcomes of our study which were compared with the ADRs that occurred among the tuberculosis patients under intermittent regimen in another study done by Mandal et al in Kolkata (Table 4). The comparison revealed that, the percentage of ADR cases were more among participants on daily regimen 36.9% than 25.6% of those on the intermittent regimen but the difference was observed to be statistically insignificant (p value 0.178). As well as the rate of ADR events that occurred among participants on daily regimen of ATT were greater (44.3%) when compared (25.6%) to that of the intermittent regimen of ATT. This difference was found to be statistically significant (p value 0.031). This also indicated that the participants on daily regimen ATT had experienced more than one ADRs during their treatment

course as compared to those on intermittent regimen of ATT in the reported study.

## DISCUSSION

The shift in treatment regimen from intermittent to daily regimen had necessitated the need for a closer observation of occurrence of ADRs. In our study there were a higher number of males (60.7%) than females (39.3%) diagnosed as new pulmonary TB cases which was similar to the global observations of 3:2 ratio.<sup>14</sup> No transgenders were reported in our study. Lesser number of transgenders were reported in RNTCP in 2018, this may be due to reluctance to disclosure their gender preferences or lack of awareness among them leading to undiagnosed cases or stigma that prevails in the society.<sup>15-17</sup> The new pulmonary TB cases of our study were reported higher among the working age groups 26-65 years (60.7%). The 2019 India TB report had also reported a higher (89%) proportion of cases among the working age groups 15-69 years.<sup>3</sup> It was observed that a higher number of participants were residing in urban areas as compared to rural areas, this could probably be due to the location of the TU in Sonipat district which predominantly comprises of urban population. Based on the personal habits of our study participants 23.0% (smoke=20.5%, smokeless=2.5%) were tobacco use, 7.4% alcohol users and none were drug abusers. Bates and colleagues, in their meta-analysis of 24 studies on the effects of smoking on tuberculosis, showed that the relative risk of tuberculosis disease (RR=2.3-2.7) was high among smokers in comparison to non-smokers with additional risk of death in persons with active tuberculosis.<sup>18</sup>

In this study the most common ADR reported was loss of appetite 13.1% followed by 8.2% flu-like symptoms, 6.6% nausea, 5.7% joint pains, 2.5% pain in abdomen, 2.5% headache, 1.6% itching and rash, 0.8% burning in hands and feet and 0.8% giddiness. Three (2.5%) patients had symptoms other (chest pain 0.8%, constipation 0.8% and persistent cough 0.8%) than the once in the programme. In a study among pulmonary tuberculosis patients on 4-FDC (four months of fixed drug combination), gastrointestinal and skin disorders were the most common adverse events (AE) which were mostly of mild or moderate severity.<sup>19</sup> Among the HIV positive pulmonary tuberculosis patients, the daily regimen group reported 27% ADRs and only 17% in intermittent regimen group.<sup>20</sup>

A study done by Sadiq et al on adverse drug reactions among tuberculosis patients reported gastro-intestinal tract as the most common ADR i.e., 67.56% followed by nervous system (10.81%).<sup>21</sup> Another study done on profile of adverse drug reactions in tuberculosis patients on ATT by Asati et al in 2016, reported more of the gastrointestinal symptoms like anorexia, vomiting and nausea among 60%, abdomen pain in 47%, headache in 29%, tingling of burning sensation of hands and feet in



22%, joint pain in 20%, fever in 20%, dermatologic manifestation in 16%. No adverse reactions were found among 8% of the patients.<sup>22</sup> A study by Nishant et al also reported gastrointestinal intolerance, arthralgia and itching with or without rashes as the most common ADRs.<sup>23</sup>

When we compared the daily regimen ADRs with the intermittent regimen used for treating tuberculosis, it was seen that in intermittent regimen group there were 25.58% adverse reactions whereas our study on daily regimen ADRs were that of 35%.<sup>24</sup> The daily regimen in contrast to intermittent regimen means the overall increase in the amount of ATT drugs for each patient. Thus, leading concerns related to cases and events of ADR. The comparison revealed that, the percentage of ADR cases were more among participants on daily regimen 36.9% than 25.6% of those on the intermittent regimen but the difference was observed to be statistically insignificant (p value 0.178). As well as the rate of ADR events that occurred among participants on daily regimen of ATT were greater (44.3%) when compared (25.6%) to that of the intermittent regimen of ATT. This difference was found to be statistically significant (p value 0.031). This also indicated that the participants on daily regimen ATT had experienced more than one ADRs during their treatment course as compared to those on intermittent regimen of ATT in the reported study.<sup>24</sup>

The most commonly reported ADRs of the first line TB drugs were reported in varying degrees.<sup>25</sup> According to the study done by Singh AK et al among two groups of patients on intermittent and daily ATT regimens it was concluded that, incidence of ADRs were more in daily regimen group (27, 54%) as compared to intermittent regimen group (12, 24%) (p-value <0.01).<sup>26</sup>

In our study on daily regimen ATT, it was observed that ADRs increased initially and later subdued that is, 16.4% of the participants during the first contact had self-reported ADRs which increased to 37.4% during second contact. During the third contact the self-reported ADRs saw a decline to 10.6% and by fourth contact to 8.0% but, no study was available in the literature for comparison. Though there were a greater number of ADRs reported none were severe and hence did not require any change in the regimen.

### Limitations

The study population was limited to one district of one state so findings cannot be generalized to larger areas. Sample size was limited to one Tuberculosis Unit and one quarter of the years which may not be sufficient to elicit rare ADRs events. ADRs were not studied in cases with comorbidities which in fact may have more/severe ADRs.

## CONCLUSION

The daily regimen though had higher ADRs as compared to intermittent regimen, the non-severity of the ADRs had not led to the change in the regimen. Hence daily regimen can be used to achieve better outcomes of new sputum positive pulmonary tuberculosis patients.

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